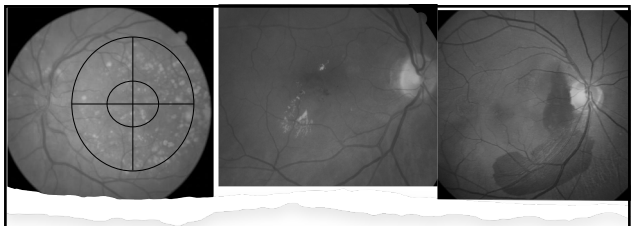

Emerging Trends in Macular Disease

Sherrol Reynolds OD, FAAO, FORS, FNAP

1

COPE Disclosure

Sherrol A. Reynolds OD, FAAO, FORS, FNAP
Professor of Optometry
Nova Southeastern University (NSU)
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Serve on the speaker bureau, advisory, or contributed board for:
Vision Service Plan (VSP), American Diabetes Association (ADA), Allergan (AbbVie Company), Genentech (Roche), Regeneron

2

Course Agenda

- Describe the essential tools in examination of macular for assessment of abnormalities leading to a proper diagnosis.
- Appreciate specific clinical and diagnostic findings of most common macular disease.
- Understand the management strategies and preferred practice guidelines for commonly encountered macular disease.
- Know the clinical course, expected outcomes, and latest research for commonly encountered macular disease.

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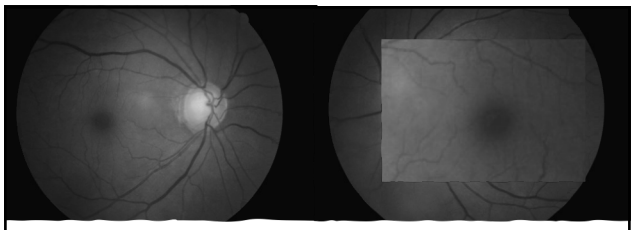

- 46-year-old Female
- CC: “Central vision defect” OS X few months
- BCVA-OD 20/20, OS 20/20

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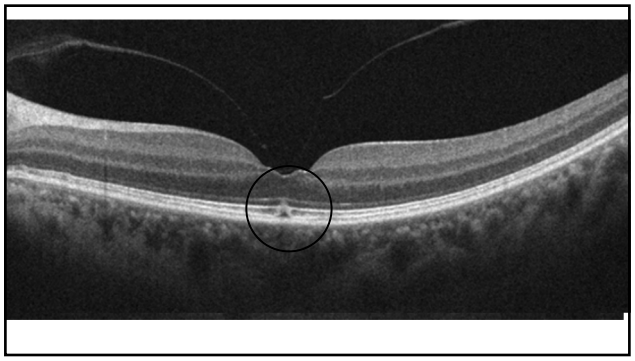

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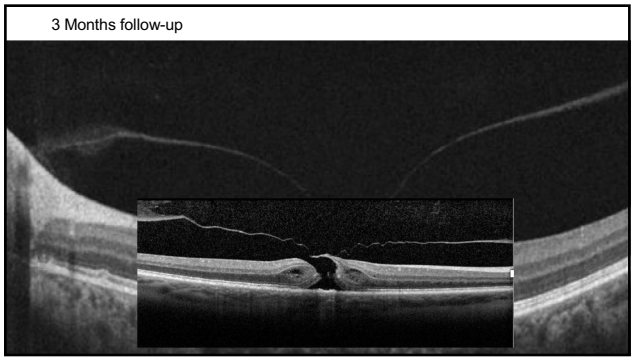

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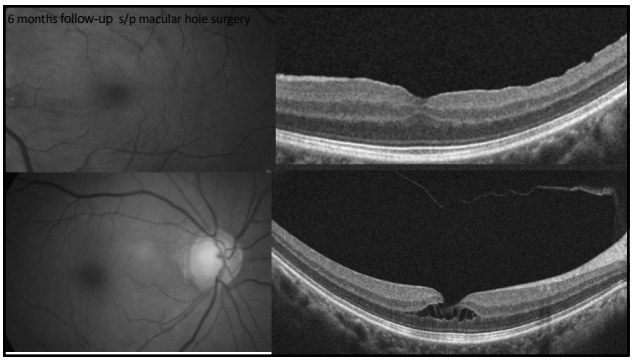

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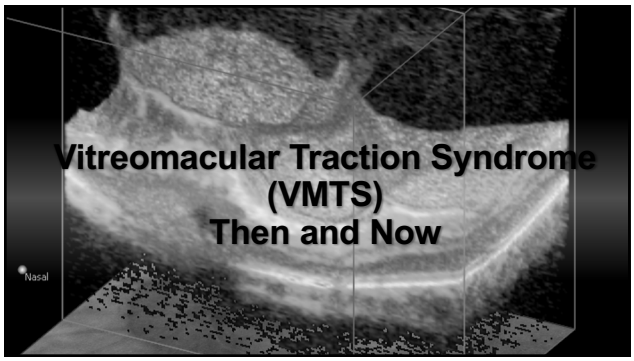

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Entity	OCT-based definition	Additional features	Symptom	Corresponds to full thickness macular hole (FTMH) stage:
Vitreomacular adhesion (VMA)	The following must be present on at least one OCT B-scan image: (i) Partial vitreous detachment as indicated by elevation of cortical vitreous above the retinal surface in the perifoveal area (ii) Persistent vitreous attachment to the macula within a 3-mm radius from the center of the fovea (iii) Acute angle between posterior hyaloid and inner retinal surface (iv) Absence of changes in foveal contour or retinal morphology		None	Stage 0 (Other eye should have full thickness macular hole)
Vitreomacular traction (VMT)	The following must be present on at least one OCT B-scan image: (i) Partial vitreous detachment as indicated by elevation of cortical vitreous above the retinal surface in the perifoveal area (ii) Persistent vitreous attachment to the macula within a 3-mm radius from the center of the fovea (iii) Acute angle between posterior hyaloid and inner retinal surface (iv) Presence of changes in foveal contour or retinal morphology (distortion of foveal surface, intraretinal structural changes such as pseudocyst formation, elevation of fovea from the retinal pigment epithelium (RPE), or a combination of any of these three features) (v) Absence of full thickness interruption of all retinal layers	Foveal pseudocyst, macular thickening, retinal capillary leakage (typically isolated VMT alone does not cause leak on fluorescein angiography), macular schisis, cystoid macular edema, retinal detachment	Reduced or distorted vision	Stage 1 (VMT only, i.e. impending macular hole) OR Stage 2 (VMT with small/medium FTMH) OR Stage 3* (VMT with medium/large FTMH)

The International Vitreomacular Traction Study Group Classification of Vitreomacular Adhesion, Traction, and Macular Hole. Ophthalmology. 2013;120(12):2611–2619

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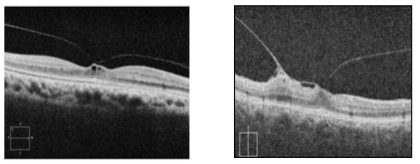
Vitreomacular Traction Study (IVTS) Group (Duker, 2013)

Vitreomacular adhesion (VMA)	(i) Focal: Width of attachment ≤1500 µm (ii) Broad: Width of attachment >1500 µm (i) Concurrent: Associated with other macular abnormalities (e.g. age-related macular degeneration, retinal vein occlusion, diabetic macular edema) (ii) Isolated: Not associated with other macular abnormalities
Vitreomacular traction (VMT)	(i) Focal: Width of attachment ≤1500 µm (ii) Broad: Width of attachment >1500 µm (i) Concurrent: Associated with other macular abnormalities (e.g. age-related macular degeneration, retinal vein occlusion, diabetic macular edema) (ii) Isolated: Not associated with other macular abnormalities



Focal VMT or V shaped J-shaped VMT

Ophthamology.2013 Dec; 120(12): 2611-9

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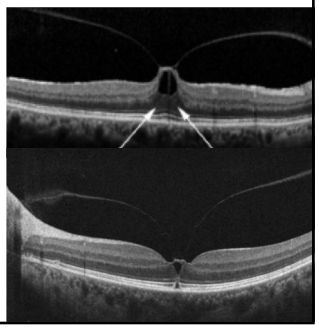
Predictors of Vitreomacular Traction Release

- VMT- Classified by the degree of i**nner-only** versus **both inner and outer** retinal involvement
- Spontaneous resolution
- **10–32% of VMT with only inner retinal distortion are more likely to have spontaneous resolution of traction compared with those who had both inner and outer retinal distortions.**



Clinical course of vitreomacular traction managed initially by observation. Ophthalmic Surg Lasers Imaging Retina 2015 46(5):571–576

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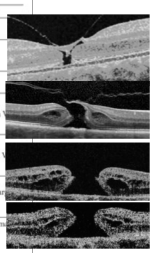
Classification of Macular Hole

TABLE 1

Gass classification	OTC findings	Classification IVTS
Stage 0	Minimal changes in the foveal contour with perifoveal detachment of the perifoveal vitreous cortex without traction	VMA
Stage 1A: imminent MH	Foveal cysts and sensory foveolar detachment associated with perifoveal detachment with traction of the posterior vitreous on the foveal internal limiting membrane	VMT
Stage 1B	Cyst in the outer retina causing rupture of the cones layer. Perifoveal detachment of posterior vitreous	VMT
Stage 2: small MH	Full-thickness MH of small diameter, with partial rupture of the internal wall of the cyst. Partial detachment of the posterior vitreous, which still remains adhered to the operculum	FTMH small/medium with V
Stage 3: large MH	MH of a larger size. Total detachment of the posterior vitreous at the level of the macular area, which persists adhered to the papilla. Occasionally, a free operculum adhered to the posterior vitreous can be seen	FTMH medium/large with V
Stage 4: full-thickness MH with PVD	Total detachment of the posterior vitreous. In some cases, the vitreous is not observed on OCT scans. Larger diameter of the hole with halo of outer retinal detachment in many occasions	FTMH small/medium/lar without TVM

FTMH: full-thickness macular hole, MH: macular hole, OCT: optical coherence tomography, PVD: posterior vitreous detachment, VMA: vitreom adhesion, and VMT: vitreomacular traction.



Journal of Ophthalmology 2015

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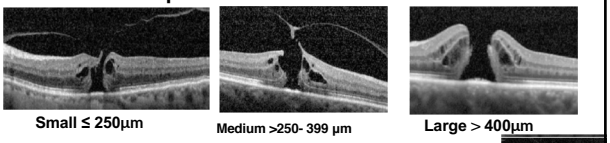
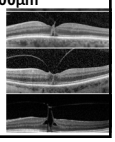
VMT/Macular Hole

Macular Hole: Updated Classification



Small ≤ 250µm | Medium >250- 399 µm | Large > 400µm

Cause -- primary or secondary/ Presence of absence of VMT



The International Vitreomacular Traction Study Group Classification of Vitreomacular Adhesion, Traction, and Macular Hole. Ophthalmology. 2013;120(12):2611–2619

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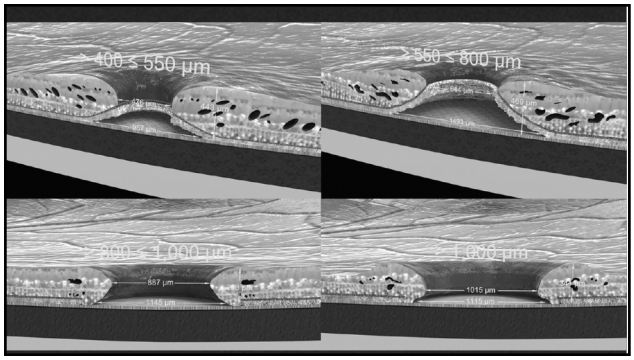

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TABLE 3. MEAN BCVA GAINS BASED ON SURGICAL TECHNIQUE (LOGMAR)

Surgical Technique	Large	X-Large	XX-Large	Giant
ILM Peeling	-0.5293	-0.4248	-0.3858	NA
ILM Flap	-0.3602	-0.3778	-0.2338	-0.2694
Macular Hydrodissection	NA	-0.4748	-0.3441	-0.5664
Human Amniotic Membrane	-0.4902	-0.5177	-0.5342	-0.3497
Autologous Retinal Transplantation	0.2202	-0.3561	-0.4633	-0.4178

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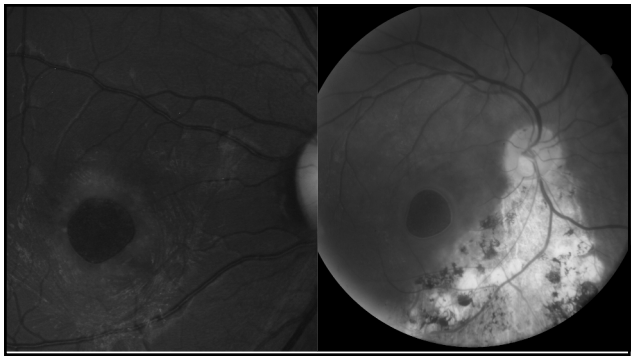

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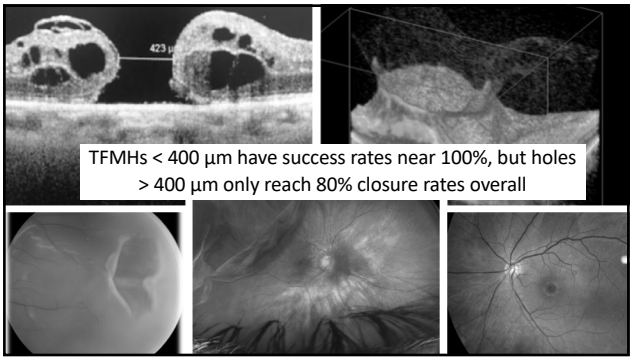

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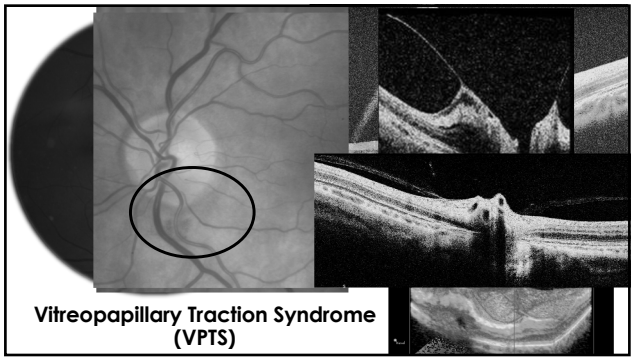

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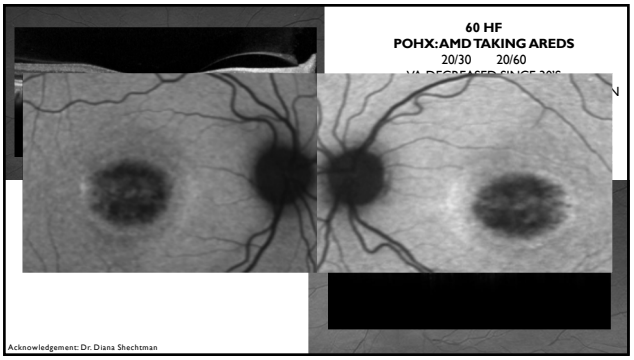

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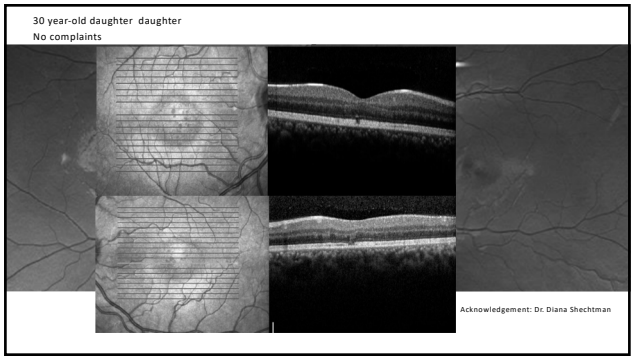

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Stargardt (STGD) disease

Stargardt macular dystrophy, juvenile macular degeneration, or fundus flavimaculatus	Common cause of central vision loss in adults under the age of 50 • Most common childhood recessively inherited macular dystrophy	Autosomal Recessive (AR) • Genetic basis due to mutations in the *ABCA4* gene
Lipofuscin storage disease- affects the RPE/photoreceptors through a sequence variant in ABCA4 gene • Mutations in this gene result in accumulation of N-retinylidene-N-retinyl-ethanolamine (A2E)	VA- between 20/50 and 20/200	Risk of CVM

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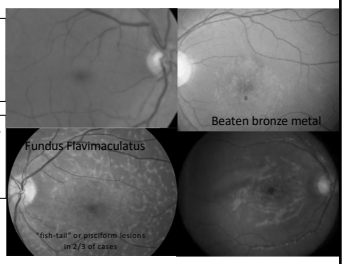
Spectrum of disease

No maculopathy	Maculopathy with/without flecks
Retinal pigment epithelium (RPE) and choriocapillaris atrophy	Yellow or white fish-shaped flecks with no associated maculopathy
Extensive atrophy (looks like RP)	



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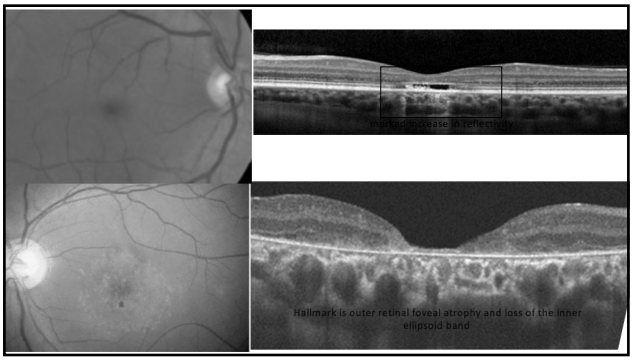

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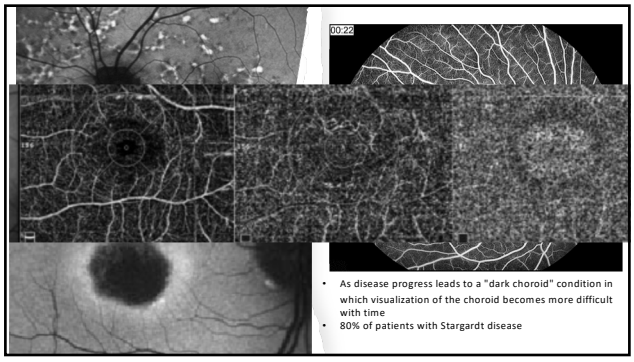

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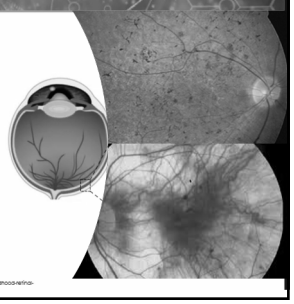
Monogenic Disease in the Eye: Inherited Retinal Diseases (IRDs)

- Family of genetic disorders that cause retinal degeneration[1]
  - Leber Congenital Amaurosis (LCA)
  - Retinitis Pigmentosa (RP)
  - Cone-Rod/Rod-Cone Dystrophy
  - Choroideremia
  - Stargardt Macular Degeneration
- **Rare** – Accurate diagnosis can be difficult and require multiple physician visits[2]
- **Few/no treatments available**[1] – Gene therapy could potentially provide new treatments



References: 1. Sahel et al. Cold Spring Harb Perspect Med. 2014;5(2):a017731. 2. AAO. https://www.aao.org/eyenet/article/childhood-retinal-hereditary...

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IRD Gene Therapy
LUXTURNATM (voretigene neparvovec-rzyl)

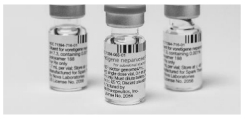
- A prescription gene therapy product used for treatment of patients with inherited retinal

Ocugen announces dosing completion in second cohort of GARDian clinical trial for Stargardt disease

OCU410ST for Stargardt Disease (GARDian)

May 20, 2024

LUXTURNA uses the adeno-associated viral Vector serotype 2 (AAV2) to carry a functional Copy of the RPE65 gene into the retinal pigment Epithelial (RPE) cells to compensate for the RPE65 mutation.



Luxturna is **$850, 000 per a one-time treatment**

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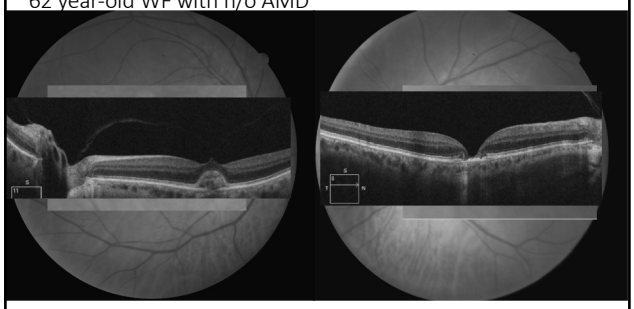
62 year-old WF with h/o AMD



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Adult-onset Macular Vitelliform Dystrophy (AVMD)

- Adult-onset foveovitelliform macular dystrophy (AFVD)
- Autosomal dominant (AD) disease
- Bilateral vitelliform (egg-like) lesions in the macula
  - closely resembles Best's disease
  - **Bestrophinopathies**
- *BEST1* mutation/ PRPH2
  - Lipofuscin deposits in the RPE layer
- Abnormal electrooculogram (EOG)
- Risk of CVM

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Clinical Stage

Stage I • Previtelliform: normal or subtle RPE changes (central honeycomb changes). Normal vision	**Stage II** • Vitelliform: classic "egg-yolk" lesion	**Stage III** • Pseudohypopyon: Layering of lipofuscin
Stage IV • Vitelleruptive: scramble egg appearance	**Stage V** • Atrophic: RPE atrophy 20/30-20/200	**Stage VI** • CNV: 20% of patients. 20/200 or worse

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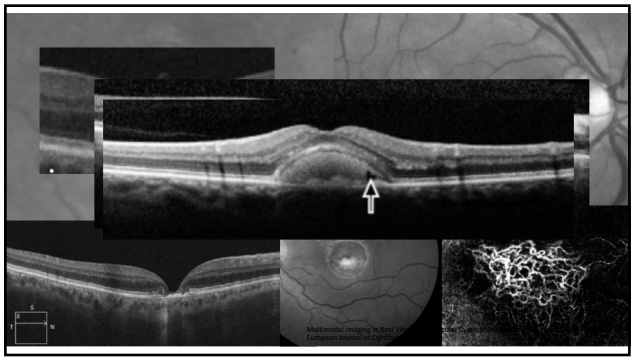

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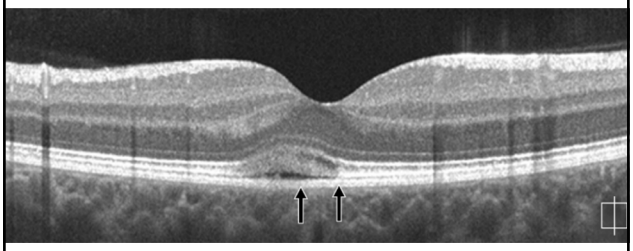
Best's Disease



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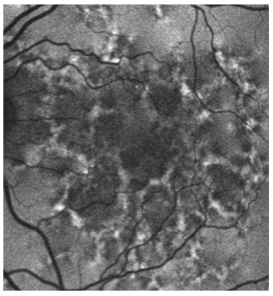

Pattern Dystrophy of the RPE

- Clinical picture
  - Symptoms vary – not correlated to maculopathy
    - **Mild** visual disturbances
      - Blurred vision, Metamorphopsia/Relative scotomas
  - Heterogenous group of A/D inherited maculopathies
    - Human retinal degeneration slow (RDS)/peripherin gene on chromosome
  - Adult-onset manifestation: **30-50 yo**

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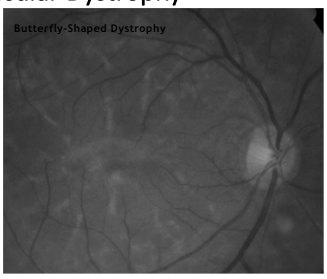
Pattern Macular Dystrophy

- Butterfly- shaped pigment dystrophy
- Reticular dystrophy of the RPE
- Multifocal pattern dystrophy
  - simulating fundus flavimaculatus



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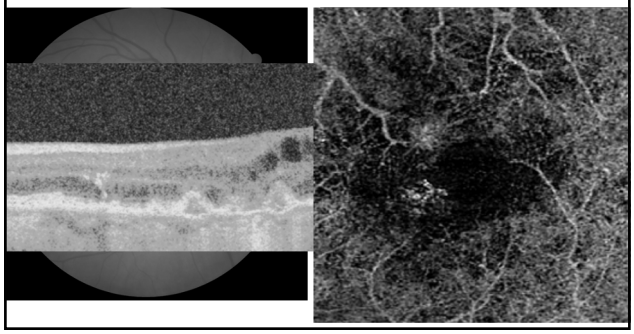

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Prevalence of Age-Related Macular Degeneration (AMD) 2024

- AMD affects ~20 million American
- 2 million Americans have Advanced AMD
  - Increase to >5 million by 2050
- 8 million Americans have Intermediate AMD
- 8 million have Geographic Atrophy (GA)

Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of age-related macular degeneration in the US in 2019. JAMA Ophthalmol. November 3, 2022

The Pathophysiology of Geographic Atrophy Secondary to Age-Related Macular Degeneration and the Complement Pathway as a Therapeutic Target. Retina. 2017;37(5):819-835

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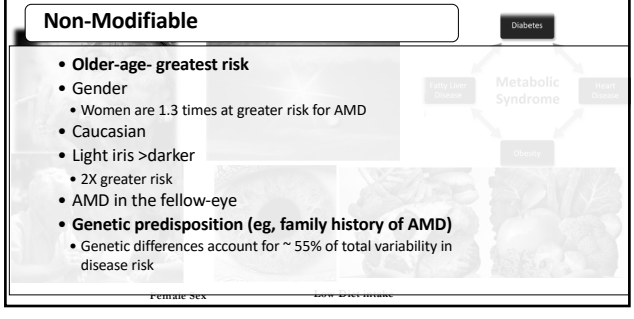
AMD – Risk Factors

Non-Modifiable

- **Older-age- greatest risk**
- Gender
  - Women are 1.3 times at greater risk for AMD
- Caucasian
- Light iris >darker
  - 2X greater risk
- AMD in the fellow-eye
- **Genetic predisposition (eg, family history of AMD)**
  - Genetic differences account for ~ 55% of total variability in disease risk



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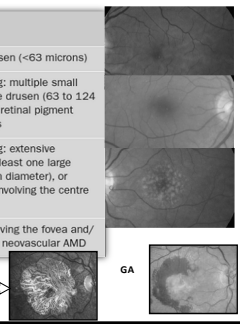
AREDS Classification of AMD

Classification	AREDS Category	Clinical signs
No AMD	1	None or a few small drusen (<63 microns)
Early AMD	2	Any or all of the following: multiple small drusen, few intermediate drusen (63 to 124 microns in diameter), or retinal pigment epithelium abnormalities
Intermediate AMD	3	Any or all of the following: extensive intermediate drusen, at least one large drusen (≥125 microns in diameter), or geographic atrophy not involving the centre of the fovea
Advanced AMD	4	Geographic atrophy involving the fovea and/or any of the features of neovascular AMD



Age-Related Study Disease Study Research Group. Arch Ophthalmol. 2005;123(11):1570-1574

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Self-reported Calcium Supplementation and Age-Related Macular Degeneration

ABSTRACT

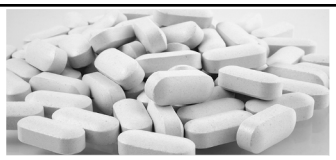
Importance: Despite widespread use of calcium supplementation among elderly people, little is known about the association between such consumption and the prevalence of age-related macular degeneration (AMD) in the United States.

Objective: To investigate (a) association between self-reported supplementary calcium consumption and the prevalence of AMD in a representative US sample.

Design, Setting, and Participants: This cross-sectional study included 5951 participants 50 years and older in the 2007-2008 National Health and Nutrition Examination Survey (NHANES) who were evaluated for the presence or absence of AMD by fundus photography. Participants were interviewed regarding use of dietary supplements and asked to bring the 30-day period preceding enrollment. Self-

800 mg per day of supplementary calcium are 85 percent more likely to be diagnosed with AMD than those who do not supplement with calcium

participants not self-reporting supplementary calcium consumption after adjusting for confounders.



Lipid-lowering agents:
- Statins: Cholesterol
- Parallels between cardiovascular disease and AMD
- Studies inconclusive

Metformin:
- Oral medication used to treat DM2
- Could prevent AMD due to potential anti-aging properties
- Antiangiogenic, anti-inflammatory, and antioxidative properties

Levodopa:
- Used to treat movement disorders (Parkinson's)
- Stimulates pigment epithelial growth factor (PEDF); has antiangiogenic properties and reduces VEGF levels
- Promising findings in studies

JAMA Intern Med. 2013;173:258-264]
Metformin Use and Age-Related Macular Degeneration in Patients Without Diabetes. JAMA Ophthalmol. 2024 Jan 1;142(1):53-57.

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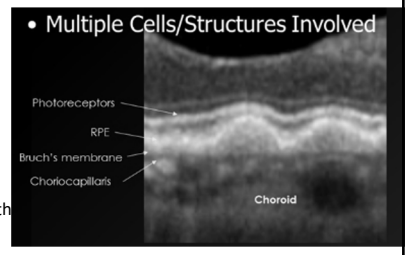
AMD Pathogenesis

- Oxidative stress to the retinal pigment epithelium (RPE)
- Reduced mitochondrial function
- Chronic low-grade inflammation of the retina
- Angiogenesis cascade
- Stress-induced cell death



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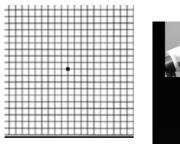
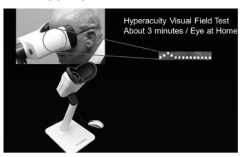
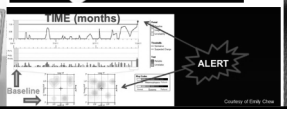
Monitoring AMD Patients

- Amsler grid
  - Low compliance
- HOME MONITORING DEVICE
  - FORESEE HOME
  - OCT HOME





FDA Grants AI-Powered Notal Vision Home OCT "SCANLY" De Novo Marketing Authorization



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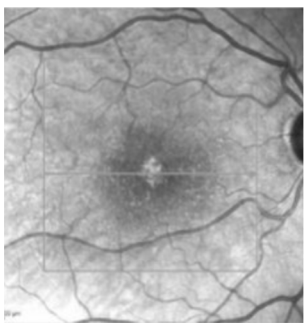

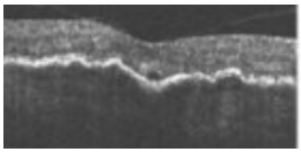

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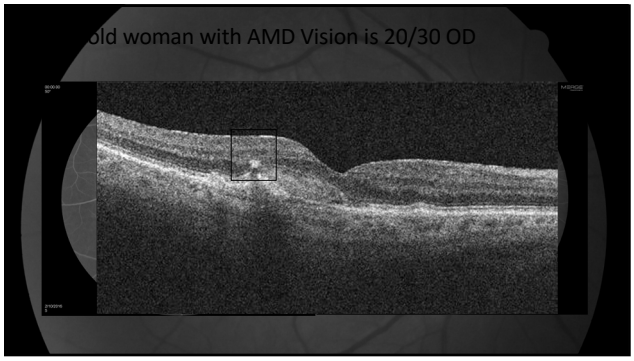

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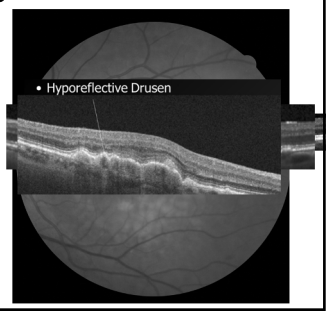
SD-OCT: AMD High Risk Features

- Loss of RPE integrity
- Disruption of Photoreceptor
- Intraretinal Hyper-reflective foci overlying druse (pigment migration)
- Hypo-reflective foci within druse ('softening of drusen)



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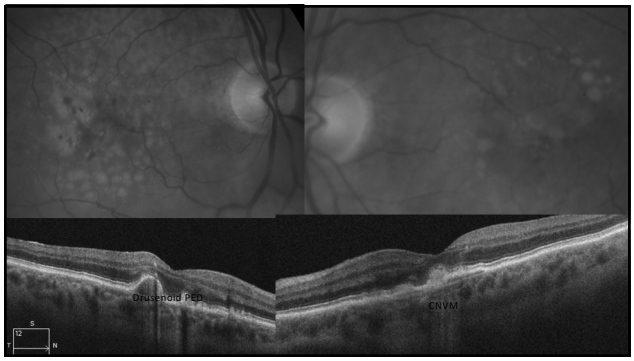

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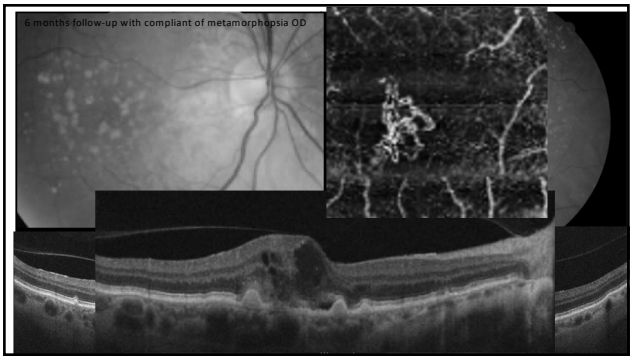

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Current ARMD Treatment Options

- Macular Photocoagulation – used Rarely – "Extra-Macular lesions"
- Photodynamic therapy – used Rarely – PCV, chronic leaking growing lesions with scars
- Macugen – used "maybe never" very ineffective but still available
- Avastin – used with step therapy and for cost reasons
- Lucentis
- Eylea (2mg) and HD Eylea (8mg)
- Brolucizumab (Beovu)- used rarely – unresponsive CNV
- Vabysmo - increasing usage due to improved duration and efficacy
- Susvimo –rarely used – new technology – few trained surgeons
- Biosimilar Lucentis – usage will start soon and be dictated by insurance

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Extended Treatment

Anti-Vegf Biosimilars

- "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
- Many in development
  - Ranibizumab ≅ 5
  - Aflibercept ≅ 8
    - Ahzantive (aflibercept-mrbb)
- Bevacizumab ≅ 1 Outlook Pharmaceuticals (Lytenava)

High Dose Aflibercept (Eylea)

- PULSAR (AMD) and PHOTON (DME) Studies
  - Looked at 8 mg vs 2 mg of Eylea
  - Demonstrated non-inferior and clinically equivalent vision gains at 48 weeks with 8 mg at 12- and 16-week dosing after 3 initial doses compared to Eylea every 8 weeks after initial dosing
- Eylea HD FDA approved 8/18/2023 for AMD, DME and DR
  - Recommended dose 1 injection every 4 weeks for first 3 months 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

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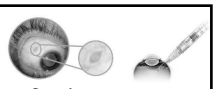
Vabysmo (faricimab)

- Roche/Genentech
  - FDA approved January 3, 2022 for AMD and DME
- First bi-phasic antibody for intraocular use
  - One arm: Vegf-A inhibitor
  - Other arm: Angiopoietin-2 (Ang-2)inhibitor
    - growth factor that promotes vascular destabilization and and inflammation
  - Dual inhibition of VEGF and Ang-2 have proven more effective than inhibiting either target alone
- Multiple studies show similar results to monthly Lucentis/Eylea but able to object less frequently, many pts q 16 weeks
- October 2023- FDA approved for RVO
  - COMINO and BALATON



Susvimo

Previously called Genentech Port Delivery System (PDS)
- Refillable port placed under conjunctiva to allow steady supply of Lucentis

Studies (LADDER, ARCHWAY) demonstrated equivalent results to monthly Lucentis at 40 weeks
- Large % of pts did not need refill prior to 6 or 12 mos

FDA approved 10/1

Recalled 10/22
- Issue with implants breaking when refilled
- **Jul 8, 2024- Genentech reintroduce Susvimo-updated the Susvimo implant and refill needle**

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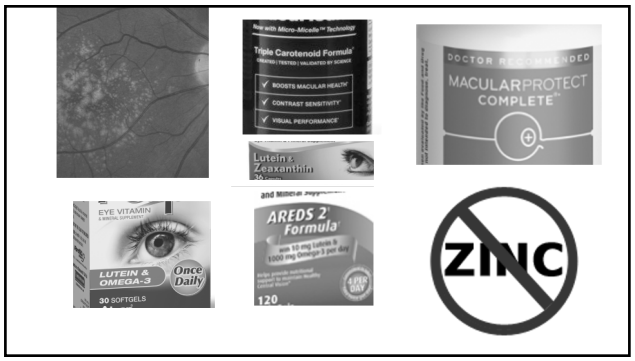

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ARVO Annual Meeting Abstract | June 2021

The Results of the 10 Year Follow-on Study of the Age-Related Eye Disease Study 2 (AREDS2)

Emily Y Chew; Traci E Clemons; Tiarnan D L Keenan; Elvira Agron; Claire E Malley; Amitha Domalpally

Purpose : To assess the long-term effects of adding lutein/zeaxanthin and omega-3 fatty acids to the Age-Related Eye Disease Study (AREDS) supplements on age-related macular degeneration (AMD) progression and adverse side-effects.

Conclusion: The 10-year Follow-on study replicated the findings of the randomized clinical trial at 5 years. Lutein/zeaxanthin, when compared with beta-carotene, had an incremental beneficial effect on progression to late AMD. Beta-carotene doubled the risk of lung cancer, providing support for lutein/zeaxanthin as a replacement of beta-carotene in the AREDS2 supplements

***80-mg dose included in the original AREDS formula remains beneficial

Methods : The AREDS2 clinical trial randomly assigned participants with bilateral termediate AMD or late AMD in one eye to lutein/zeaxanthin and/or omega-3 fatty :ids or placebo. Secondary randomization also evaluated varying doses of beta- rotene (0 vs. 15 mg) and zinc (25 vs. 80 mg). At the end of the clinical trial, a llow-up study was conducted with 6-monthly telephone calls to the surviving REDS2 participants from the central coordinating center to collect outcome data id adverse events for safety monitoring for an additional 5 years. Medical records ere obtained from treating physicians to validate any self-reported diagnosis or treatment of late AMD and cataract and side-effects. AREDS2 supplements with lutein/zeaxanthin, vitamin C and E, and zinc plus copper were provided to all participants during this additional follow-up. Repeated measures logistic regression was used in the primary analyses.

Results : 6360 study eyes (3887 participants) were analyzed and 3047 (48%) progressed to late AMD. The main effects of lutein/zeaxanthin vs. no lutein- zeaxanthin and of omega-3 fatty acids vs. no omega-3 fatty acids resulted in hazard ratios of 0.91 (95% CI: 0.89-0.99) (p=0.03) and 1.00 (0.92-1.09) (p=0.91), respectively. When the lutein/zeaxanthin main effect analysis was restricted to those randomized secondarily to beta-carotene, the HR was 0.80 (0.69-92) (p=0.003). On direct analysis of lutein/zeaxanthin vs. beta-carotene, the HR was 0.85 (0.74-0.98) (p=0.026). For the comparisons of low vs. high zinc and no beta-carotene vs. beta-carotene, the HRs were 1.04 (p=0.48) and 1.04 (p=0.50), respectively. For those randomized to beta-carotene, the odds ratio (OR) of developing lung cancer was 1.92 (1.11-3.31)(p=0.02) while the OR for those randomized to lutein/zeaxanthin was 1.19 (0.82-1.73) (p=0.35).:

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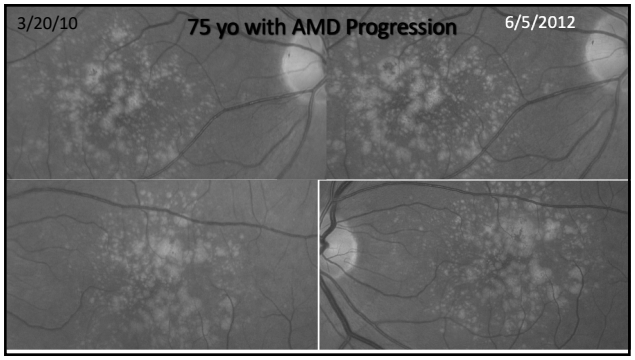

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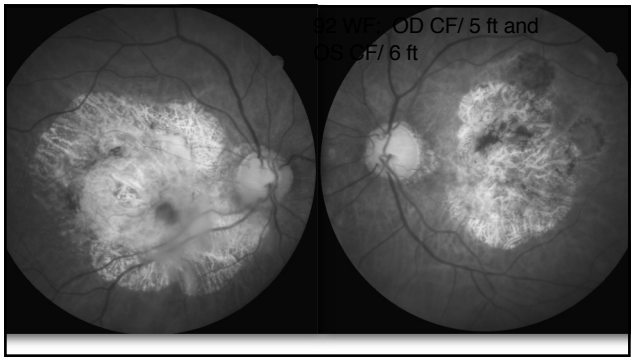

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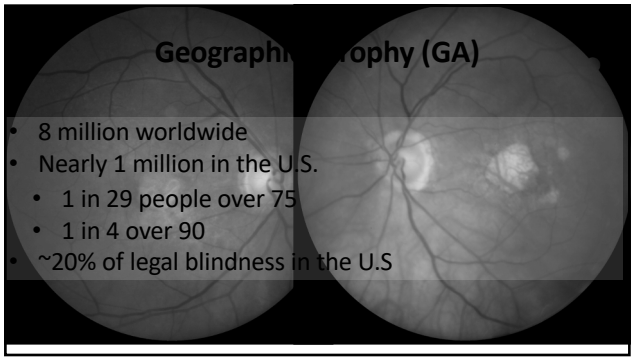

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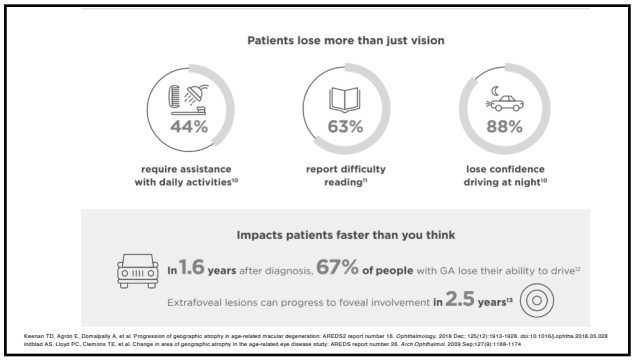

Keenan TD, Agrón E, Domalpally A, et al. Progression of geographic atrophy in age-related macular degeneration: AREDS2 report number 16. *Ophthalmology*. 2018 Dec; 125(12):1913-1928. doi:10.1016/j.ophtha.2018.05.028
Indbad AS, Lloyd PC, Clemons TE, et al. Change in area of geographic atrophy in the age-related eye disease study: AREDS report number 26. *Arch Ophthalmol*. 2009 Sep;127(9):1168-1174

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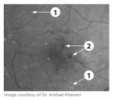
GA Progression- Classification of Atrophy Meeting (CAM)

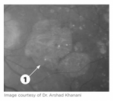
Color fundus photography (CFP)

Can be used to establish a baseline and detect pigmentary changes as AMD progresses to GA.[1]



Intermediate AMD

1. Increase in number of intermediate (63-124 µm) drusen[4]
2. Areas of pigmentary change associated with RPE abnormalities[4]

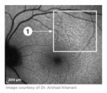


Advanced AMD (GA)

1. GA lesion border is sharply demarcated with increased choroidal vessel visibility

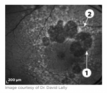
Fundus autofluorescence (FAF)

Used for diagnosis and monitoring progression by measuring the full area affected by GA.[1] FAF is a useful tool for visualizing progression when educating patients.



Intermediate AMD

1. Reticular pseudodrusen appearing as multiple, clustered, regularly networked, round areas of low-contrast hypoautofluorescence and may be prognostic of advancing GA[1,12]



Advanced AMD (GA)

1. An area of hypoautofluorescence with a sharply demarcated border indicative of atrophic lesions[4]
2. Abnormal patterns of hyperautofluorescence surrounding atrophic lesions can indicate excessive lipofuscin accumulation that may reflect cellular disfunction and is prognostic of GA progression[4]

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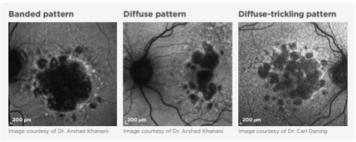
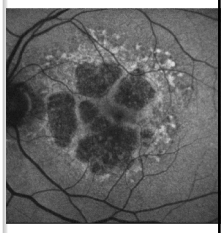
Lesion characteristics can predict rate of progression

Hyperautofluorescent FAF patterns can be predictive of the rate of GA progression. Rate of progression is slowest with no hyperautofluorescence or a focal pattern, and highest with banded and diffuse patterns. Eyes with diffuse-trickling patterns may also progress relatively quickly.[4]





Leveraging imaging in the early detection of GA is important with the potential of future treatments on the horizon.

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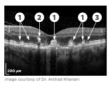
Optical coherence tomography (OCT)

Established as the standard base or reference modality in the early diagnosis of GA.[4,5]

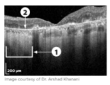


Intermediate AMD

1. Intermediate (63-124 µm) and large (≥125 µm) drusen[4]
2. Hyperreflective foci correspond to disruption of the RPE[13]
3. Detectable photoreceptor degradation

The transition from intermediate AMD to GA is a critical time in progression.

New OCT findings in patients with AMD may help determine the transition to GA and further aid in the development of a proper management plan to help preserve functional vision.

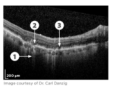


Advanced AMD (GA)

1. Choroidal hypertransmission
2. RPE, photoreceptor, and choriocapillaris layer loss

iRORA vs cRORA

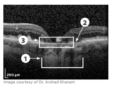
Incomplete RPE and outer retinal atrophy (iRORA), also known as nascent GA in the absence of choroidal neovascularization, represents an earlier phase of disease progression before advancing to complete RPE and outer retinal atrophy (cRORA).[6]



iRORA[6]

1. Some hypertransmission present in the choroid, but it is discontinuous
2. A corresponding zone of attenuation and disruption of RPE with persistence of basal laminar deposits
3. Photoreceptor degeneration

cRORA is a more advanced stage of atrophy.[7]



cRORA[6,*]

1. Area of choroidal hypertransmission ≥250 µm
2. Zone of attenuation/disruption of RPE ≥250 µm
3. Evidence of overlying photoreceptor degeneration, which includes ONL thinning, ELM loss, and EZ/IZ loss

*Absence of scrolled RPE or other signs of an RPE tear.

TIP: Proper optimization of instrumentation can minimize artifacts and improve the quality of imaging.[14] Work with your imaging partner to configure your instrument to your needs and specifications.

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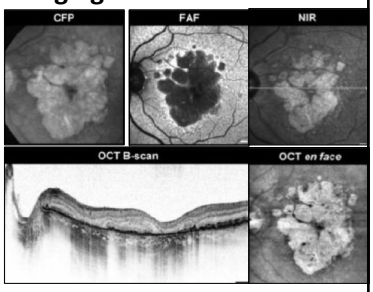
Multimodal Imaging of GA lesions

- Color fundus photography (CFP)
- Fundus autofluorescence (FAF)
- OCT
  - Near-infrared reflectance (NIR)
  - Cross sectional B-scan (line raster)
  - En-face



Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT Classification of Atrophy Report 3. Ophthalmology. 2018. 125(4). 537-548

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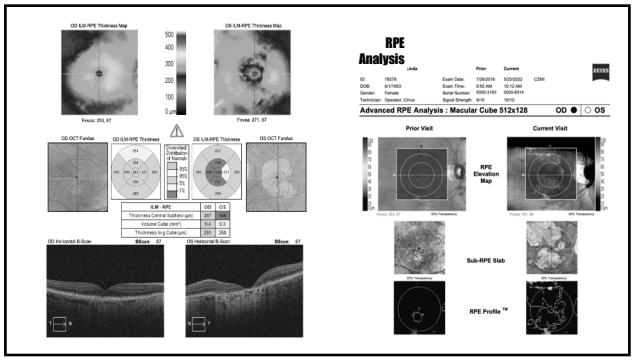

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Incomplete RPE and Outer Retinal Atrophy (iRORA)

OR

Complete RPE and Outer Retinal Atrophy (cRORA)

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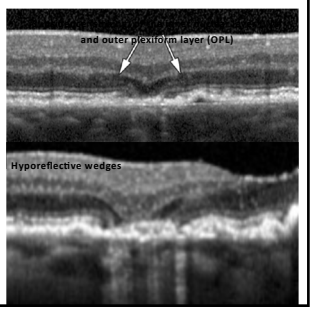
Incomplete RPE and Outer Retinal Atrophy (iRORA)

"Impending GA"
- Subsidence of the OPL & INL and a hypo-reflective wedge
- Signal hypertransmission into the choroid with corresponding attenuation/disruption of the RPE



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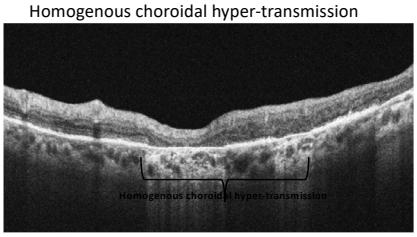
Complete RPE and Outer Retinal Atrophy (cRORA)

Absence of the RPE and photoreceptors
≥ 250µm in diameter
Homogenous choroidal hyper-transmission



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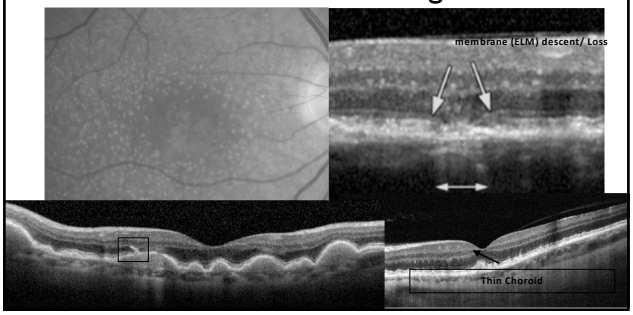
OCT Biomarker for GA Progression



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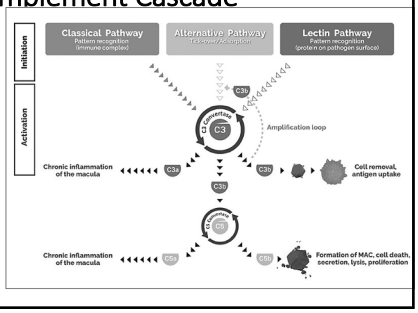
Complement Cascade

- Immune response to recognize and remove pathogens
- The cascade is made up of over 50 proteins
  - These proteins make up the membrane attack complex



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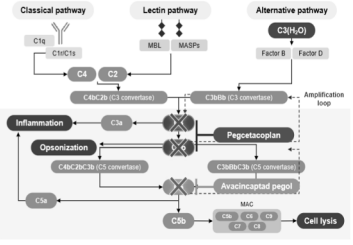
Complement Inhibitors for GA: Pegcetacoplan vs ACP

Pegcetacoplan	Avacincaptad pegol (ACP)
Targets C3 and C3b[1,2]	Targets C5[3]
Slows GA progression based on two 24-month, phase 3 OAKS and DERBY trials[3] (N=1258)	Reduced GA growth at Month 24 in phase 3 GATHER2 trial[4,5] (N=448)
In BOTH nonsubfoveal and subfoveal GA lesions	In nonsubfoveal GA lesions
With BOTH monthly and every-other-month dosing	With monthly and monthly to every-other-month dosing
Increasing efficacy over time	
Increased CNV with all complement inhibitors	

Pegcetacoplan binds to C3 and C3b, regulating the overactive complement system[6–10]



ACP, avacincaptad pegol; C3, complement component 3; C5, complement component 5; GA, geographic atrophy; MAC, membrane attack complex; MASP, MBL-associated serine protease; MBL, mannose-binding lectin.

1. Berger N, et al. *J Med Chem*. 2018;61(14):6153–6182. 2. Liao DS, et al. *Ophthalmology*. 2020;127:186–195. 3. Heier JS, et al. Presented at Retina Society 2022. 4. Jaffe GJ, et al. *Ophthalmology*. 2021;128:576–586. 5. Khanani AM, et al. Presented at American Academy of Ophthalmology 2022. 6. Boyer DS, et al. *Retina*. 2017;37:819–835. 7. Holers VM. *Ann Rev Immunol*. 2014;32:433–459. 8. Dunkelberger JR, Song WC. *Cell Res* 2010;20:34–50. 9. Strunz T, et al. *Sci Rep*. 2020;10:1584. 10. Anderson DH, et al. *Am J Ophthalmol*. 2002;134:411–431.

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Latest Treatment for Geographic Atrophy (GA)

Syfovre (pegcetocoplan)	Izervay (avancincaptad pegol)
• Apellis	• Iveric Bio (Astellas Pharma)

• FDA approved Feb 17, 2023
  • One injection every 25 to 60 days
	• FDA approved Aug 5, 2023
	  • One injection per mos for up to 12 mos

• Slows progression of GA lesions by blocking C3
  • OAKS Study: 22% qm, 18% qom
  • DERBY: 18% qm, 17% qom
  • Increasing effect with time
	• Slows progression of GA by blocking C5
	  • GATHER1/GATHER 2 studies:
	  • At 12 mos, 27% (2 mg) and 28% (4 mg) less GA growth
	  • At 18 mos, 28% and 30%
	  • Reduced rate of vision loss noted
	  • Good safety profile

• Recent concern of vasculitis	

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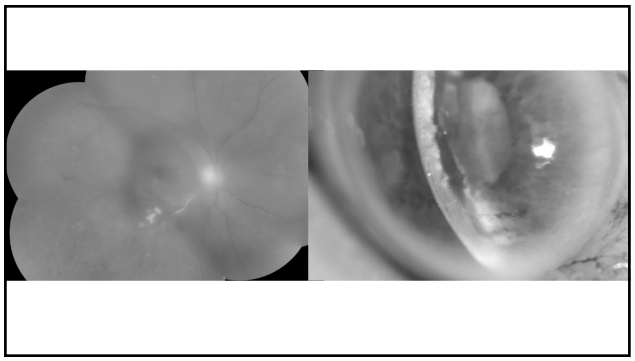

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All cases after the first injection.

Presentation: 8-23 days

VA at baseline: 20/30-5/200

VA at last FU 20/70-NLP

Sage Journals

Original Manuscripts

Retinal Vasculitis After Intravitreal Pegcetacoplan: Report From the ASRS Research and Safety in Therapeutics (ReST) Committee

Andre J. Witkin, MD, FASRS, Glenn J. Jaffe, MD, Sunil K. Srivastava, MD, Janet L. Davis, MD, and Judy E. Kim, MD, FARVO, FASRS and the ReST Committee

100%with AC inflammation 86% with vitritis.

Veins affected 100%, arteries 73% and 86% retinal hemorrhages.

68

Gene therapy in AMD: Promises and challenges

- Gene therapy are now being investigated for AMD
- Significant challenges remain, particularly with delivering the vector to the back of the eye
- Long-term benefit of gene therapies in AMD remains to be seen

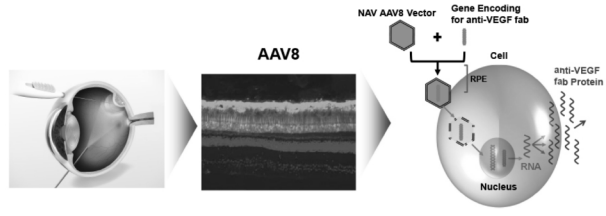
Table. Investigative gene therapies for age-related macular degeneration

Therapy name (sponsor)	Vector	Indication	Study Phase	Mechanism of action	Delivery method
RGX-314 (RegenxBio)	AAV8	Neovascular AMD	I/IIa	Encodes an anti-VEGF Fab protein similar to ranibizumab.	Surgical subretinal injection
ADVM-22 (Adverum Biotechnologies)	AAV2	nAMD	I	Promotes production of aflibercept protein.	Intravitreal injection
AAV2-sFLT01 (Sanofi/ Genzyme)	AAV2	nAMD	I	Encodes sFLT-1 to neutralize vascular endothelial growth factor.	Intravitreal injection
AAVCAGsCD59 or HMR59 (Hemera Biosciences)	AAV2	nAMD and non-nAMD	I	Soluble form of CD59 to inhibit membrane attack complex formation.	Intravitreal injection
GT005 (Gyroscope Therapeutics)	AAV2	Non-nAMD	I/II	Targets complement cascade.	Surgical subretinal injection

Heier JS, Kherani S, Desai S, et al. Intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration. A phase 1, open-label trial. Lancet. 2017;390:50-61.
Rakoczy EP, Lai C-M, Magno AL, et al. Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a Phase 1 randomised clinical trial. Lancet. 2015;386:2395-2403.
Constable IJ, Lai C-M, Magno AL, et al. Gene therapy in neovascular age-related macular degeneration: Three-year follow-up of a phase 1 randomized dose escalation trial. Am J Ophthalmol. 2017;177:150-158.
Rakoczy EP, Magno AL, Lai C-M, et al. Three-year follow-up of Phase 1 and 2a rAAV.sFLT-1 subretinal gene therapy trials for neovascular age-related macular degeneration. Am J Ophthalmol. 2019;208:113-123.
Grishanin R, Vuillemenot B, Sharma P, et al. Preclinical evaluation of ADVM-022, a novel gene therapy approach to treating wet age-related macular degeneration. Mol Ther. 2019;27:118-126.

69

RGX-314 Uses a Novel AAV8 Vector to Deliver an anti-VEGF Fab



Subretinal Procedure | Efficient Gene Delivery to the RPE[1] | RGX-314 is Designed to Deliver a Gene Encoding for an Anti-VEGF Fab Protein

70

St

- Photorec Biodegra
  - Rough
- Authenti Scaffold
- Combine on Biode

Cell Source
Induced Plu
CD34+ patient
Tissue
Not Ski
Not Embryo Recipie Issues,
Not Mesenchymal Stem Cells Obtained Via Liposuction

> Int Ophthalmol Clin. 2024 Jan 1;64(1):21-33. doi: 10.1097/IIO.0000000000000510. Epub 2023 Dec 26.

AMD and Stem Cell-Based Therapies

Joseph C Giacalone, David H Parkinson, Daniel A Balikov, Rajesh C Rao

PMID: 38146879 PMCID: PMC10783850 (available on 2025-01-01)
DOI: 10.1097/IIO.0000000000000510

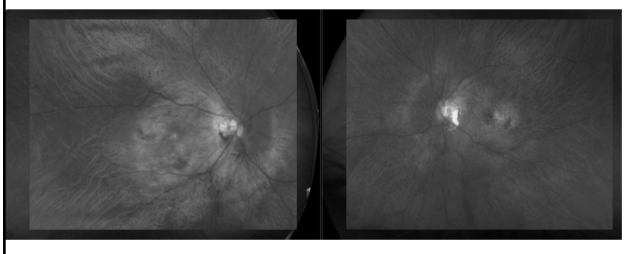
Abstract

Age-related macular degeneration (AMD) is a prevalent and complex disease leading to severe vision loss. Stem cells offer promising prospects for AMD treatment as they can be differentiated into critical retinal cell types that could replace lost host retinal cells or provide trophic support to promote host retinal cell survival. However, challenges such as immune rejection, concerns regarding tumorigenicity, and genomic integrity must be addressed. Clinical trials with stem cell-derived retinal pigment epithelial cells have shown preliminary safety in treating dry AMD, but improvements in manufacturing and surgical techniques cell delivery are needed. Late-stage AMD poses additional hurdles, possibly requiring multi-layered grafts. Advancements in automation technologies and gene correction strategies show potential to enhance iPSC-based therapies. Stem cell-based treatments offer hope for AMD management, but further research and optimization are essential for successful clinical implementation.

71

71 WM with c/o wavy vision ODX one week

20/80 (NIPH)OD 20/100 (NIPH) OS



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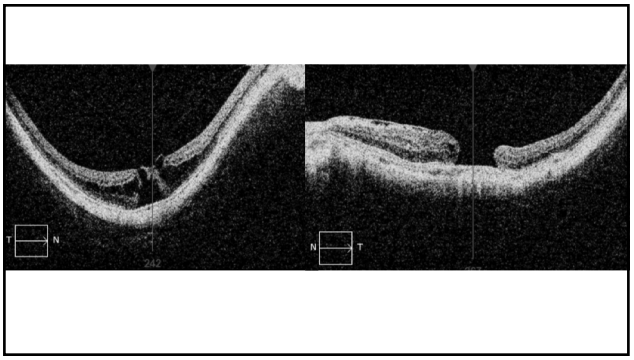


73

Additional Information:

Rx

•OD: -17.75-2.00 X 180---- 20/80 (NIPH)

•OS: -18.50 DS ---- 20/400 (NIPH)

74

Myopia 2024

Non-pathologic myopia

- Usually minimal to moderate (< 6.00 diopters)
- "high myopia"

Pathologic myopia

- (≥-6.00D)
- Axial length ≥26.5 mm
- Major cause of visual impairment worldwide
- 3% of the world's population
  - Highest prevalence in Asian populations
- A common cause of legal blindness in young individuals

Task Force on Myopia. Reducing the global burden of myopia by delaying the onset of myopia and reducing myopic progression in children: The Academy's Task Force on Myopia. Ophthalmology. 2021;128(6):816-826.

75

Nearly a 2-Fold Increase in 30 years

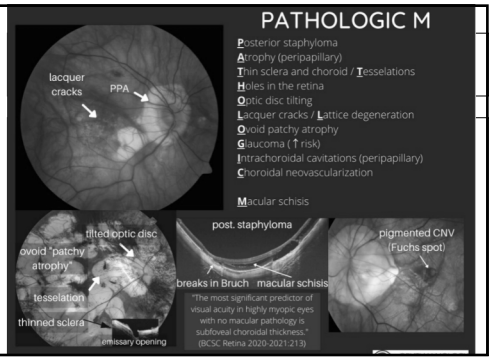
Prevalence of Myopia

By 2050, about half of the world's population is predicted to be myopic

Source: Nemeth, I., Tapasztó, B., Aclimandos, W. A., Kestelyn, P., Jonas, J. B., De Faber, J. T. H., ... & Resnikoff, S. (2021). Update and guidance on management of myopia. European Society of Ophthalmology in cooperation with International Myopia Institute. European Journal of Ophthalmology.

76

Risk Factors



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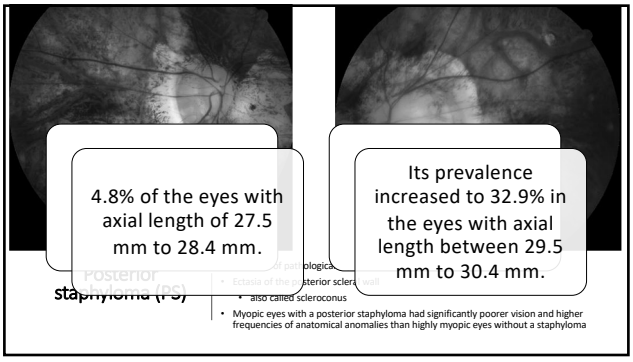

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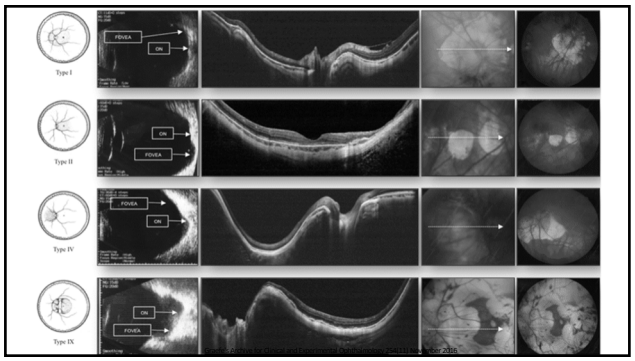

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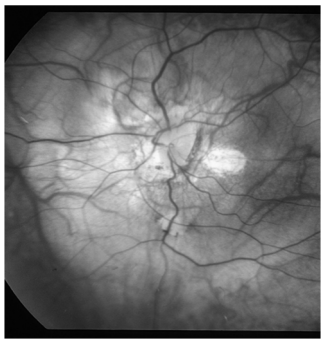
Myopic Choroidal Atrophy

- Tessellated fundus
- Diffuse choroidal atrophy
- Patchy choroidal atrophy
- Macular hemorrhage



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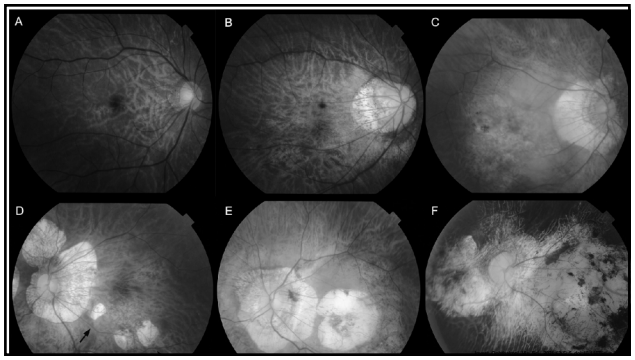

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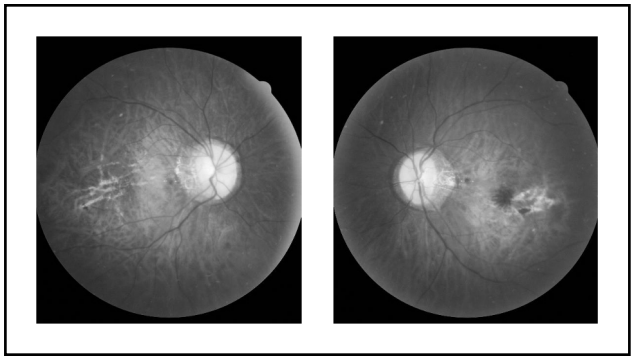

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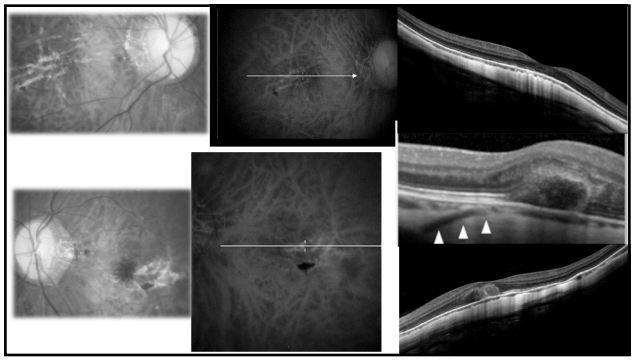

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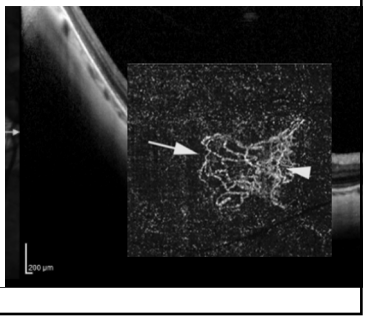
Myopic CNVM

- Develop in 10% of high myopic patients
  - CNV is higher in eyes with lacquer cracks (29 %)
- 30% of the patients who have CNVM in one eye eventually develop CNVM in the other eye
- Generally-very small-sized and show a slightly edematous appearance
- Anti-VEGF
  - RADIANCE, BRILLIANCE, MYRROR, and SHINY



Am J Ophthalmol 2014;157:9–25

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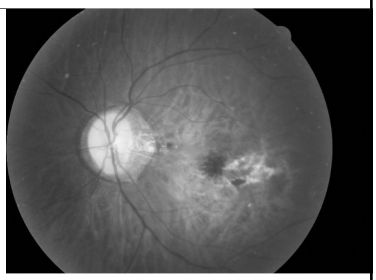
Myopic CNV

Three phases

- Active phase with proliferation of a fibrovascular membrane including CNV, exudation, and hemorrhage
- Scar phase exemplified by a Fuchs spot
- Atrophic phase



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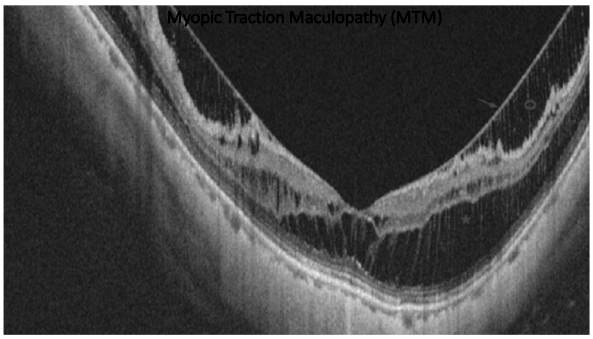

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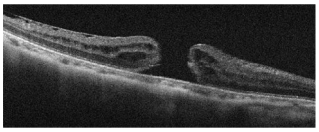
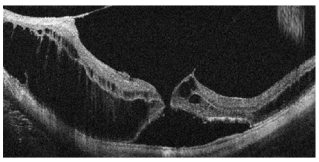
Myopic Macular hole

Two types of macular holes in highly myopic eye

1. One is the type with the edge of the hole thickened with retinal cysts
2. Myopic foveoschisis





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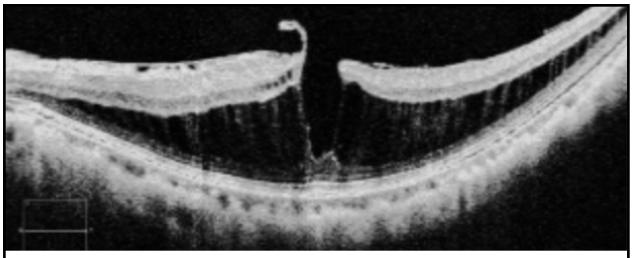
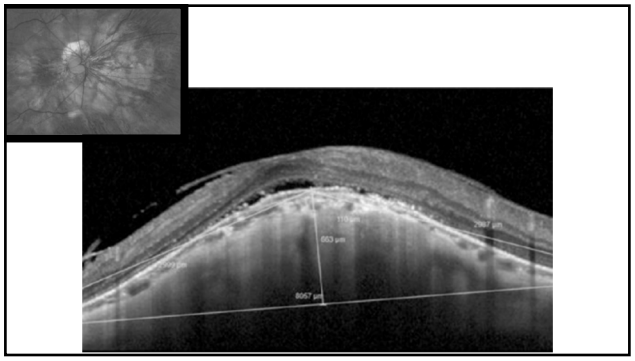


Myopic foveoschisis

- Myopic macularschisis
- Vitreoretinal interface (VRI) traction
- First described by Takano and Kishi in 1999
- Splitting in the inner nuclear layer and outer plexiform layer

88



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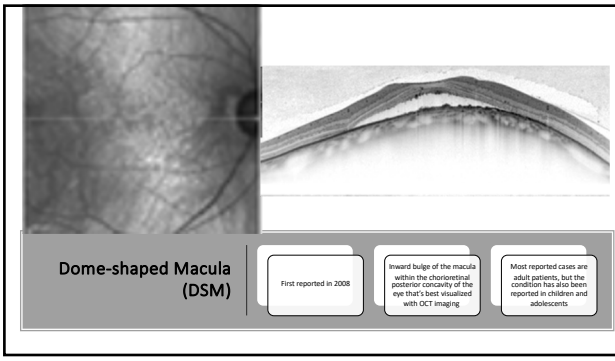

90

Dome-shaped Macula (DSM)

Complications include macular serous retinal detachment (SRD)

SRD is more commonly observed when the bulge height is greater than 350 microns and in eyes with vertical oval dome-shaped macula

RPE detachment and polypoidal choroidal vasculopathy

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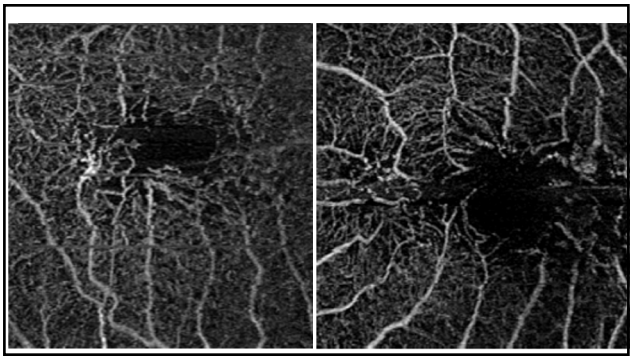

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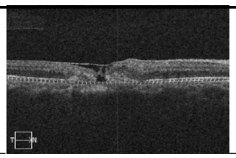
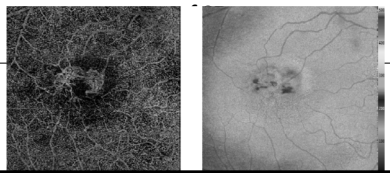


NOTE IMT 2 can be proliferative : OCTA can help in evaluation



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Macular Telangiectasia

- Poorly Understood Degenerative Retinal Disorder
- Chronic, usually Slowly Progressive Neurodegeneration
  - Perifoveal Capillary Abnormalities
    - Vascular inflammation and capillary alteration
  - Loss of outer nuclear and ellipsoid zone
  - Cystic cavitation-like changes resulting in macular thinning and macular hole formation
    - Atrophic changes start in the outer retina leading to intraretinal loss formation of partial or full-thickness macular holes differ from VM interface
  - May result in the choroidal neovascular formation
- Risk Factors
  - Genetic
  - Association with Diabetes, HTN, Obesity

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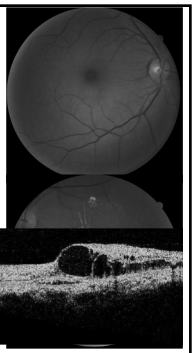
Macular Telangiectasia

- Subtypes
  - Type 1
    - Congenital, Unilateral, maybe a variant of Coat's Disease (Developmental Anomaly)
  - Type 2 (AKA Mac Tel type 2)
    - Most common, bilateral
    - Genetic- Reported cases in families including identical twins
    - Age: 30-60
  - Type 3
    - Rare and poorly understood retinal vascular disorder
- DDX: RVO, DR, Radiation Retinopathy, AMD nAMD



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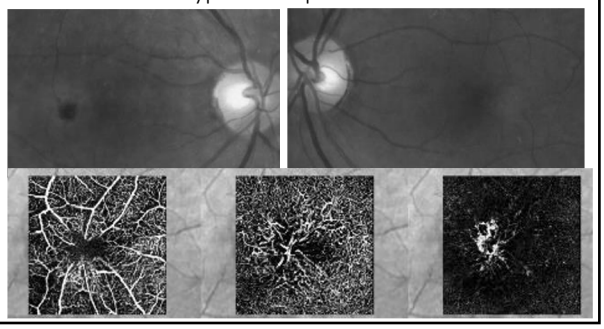
MacTel type 2 Complications



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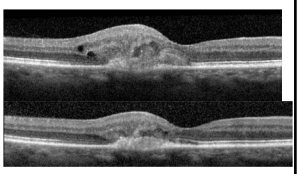
Management and Prognosis

- Focal laser and PDT (Type 1)
- Steroid Injections
  - Reduce Inflammation and Fluid but does not reverse outer retinal loss
- Anti-VEGF
  - For CNVM
  - Improves fluid but does not reverse outer-retinal loss
- Ciliary neurotrophic factor (CNTF)
  - Under Investigation



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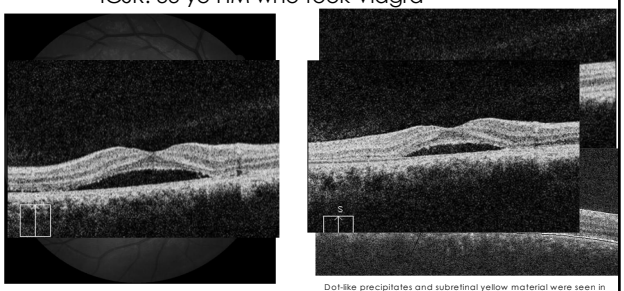
ICSR: 33 yo HM who took Viagra



Dot-like precipitates and subretinal yellow material were seen in 65% of cases with central serous chorioretinopathy that also showed high reflectivity

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Central Serous Chorioretinopathy (CSCR)

Fourth most common retinopathy

Classification

- Acute
  - Isolated or multifocal RPE or serous detachment(s)
  - Bullous serous retinal detachment
- Chronic CSCR
  - Retinal pigment epithelium depigmentation

Etiology

- Type A personality-catecholamine release, which increases choroidal permeability
- Psychological stress and depression, sleep apnea, medications (steroids, MEK inhibitors, pseudoephedrine, Methylenedioxymethamphetamine (MDMA) or ecstasy, sildenafil), *H. pylori* infection, HTN, endocrine disorders

Recurrences

- Recurrence reported to be as high as 50%

Central serous chorioretinopathy. Ophthalmologica 2014; 232: 65–76

99

Table 1 Proposed Multi-modal imaging-based central serous chorioretinopathy classification by the CSC International Group.

From: Pachychoroid disease: review and update

Simple Total area of RPE alterations ≤2 DA	Primary First known episode of SRF			±CNV
	Recurrent Presence of SRF with history or signs of resolved episode(s)	±Persistent SRF > 6 months	±Outer retinal atrophy ONL thinning ± ELM disruption ± EZ attenuation	
	Resolved Absence of SRF			
Complex Total area of RPE alterations >2 DA or multifocal	Primary First known episode of SRF	±Persistent SRF > 6 months	±Outer retinal atrophy ONL thinning ± ELM disruption ± EZ attenuation ±Intraretinal fluid	
	Recurrent Presence of SRF with history or signs of resolved episode(s)			
	Resolved Absence of SRF			
Atypical	Bullous variant, RPE tear, association with other retinal diseases			

RPE retinal pigment epithelium, *DA* disc areas, *SRF* subretinal fluid, *ONL* outer nuclear layer, *ELM* eternal limiting membrane, *EZ* ellipsoid zone, *CNV* choroidal neovascularization.

Cheung, C.M.G., Daniongani, K.K., Kiziumi, H. et al. Pachychoroid disease: review and update. *Eye* (2024)

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Pachychoroid Disease Spectrum (PDS)

Central Serous Chorioretinopathy (CSCR)	Pachychoroid Pigment Epitheliopathy (PPE)	Pachychoroid Neovasculopathy (PNV)	Polypoidal Choroidal Vasculopathy (PCV)
Peripapillary Pachychoroid Syndrome (PPS)	Focal Choroidal Excavation (FCE)	Peripapillary Pachychoroid Neovasculopathy	Peripheral Exudative Hemorrhagic Chorioretinopathy

B Brown R, Mohan S, Chhablani J. Pachychoroid Spectrum Disorders: An Updated Review. J Ophthalmic Vis Res. 2023 Apr 19;18(2):212-229.

B Brown R, Mohan S, Chhablani J. Pachychoroid Spectrum Disorders: An Updated Review. J Ophthalmic Vis Res. 2023 Apr 19;18(2):212-229 Update on Viral Gene Therapy Clinical Trials for Retinal Diseases. Shun-Yun Cheng and Claudio Punzo. Human Gene Therapy 2022 33:17-18, 843-878

Cheung, C.M.G., Daniongani, K.K., Kiziumi, H. et al. Pachychoroid disease: review and update. *Eye* (2024)

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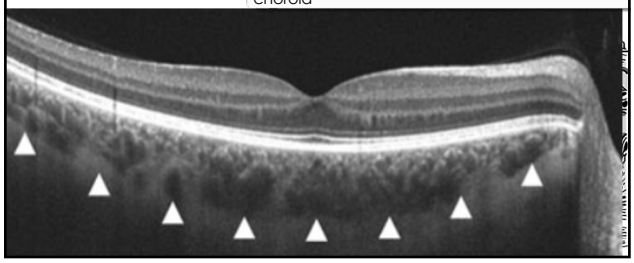
Choroidal Morphology

- posterior pole
- Typically, thickest beneath the fovea, where its average thickness is 320μm
- The temporal choroid is thicker than the nasal choroid



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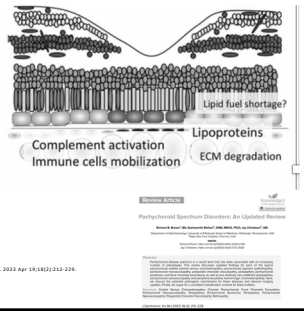
Pachychoroid Disease Spectrum (PDS)

Pachychoroid = thicken choroid

- Abnormal and permanent increase in choroidal thickness
  - (choroidal thickness of >320 µm)
- Larger Haller layer vessels (**Pachyvessels**) and medium vessels of Sattler layer & choriocapillaris present or effaced (atrophy)
- Reduced fundus tessellation- thinning of the overlying inner choroid
- Retinal pigment epithelium (RPE) abnormalities
- Choroidal vascular hyperpermeability (CVH)
- A lack of soft-drusen (an exception is made for pachydrusen, which are irregular, scattered yellow–white deposits across the posterior pole)



B Brown R, Mohan S, Chhablani J. Pachychoroid Spectrum Disorders: An Updated Review. J Ophthalmic Vis Res. 2023 Apr 19;18(2):212-229.

Gallego-Pinazo R, et al. Med Hypothesis Discov Innov. 2014;3(4):111-116.

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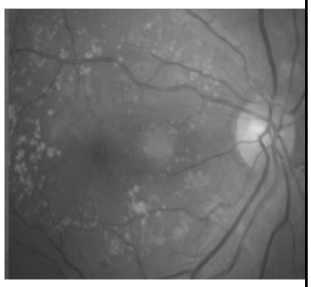
Pachydrusen

- Pachydrusen are large
  - Typically, >125 µm)
  - sub-RPE deposits that are yellow-white in color
- Deposits are distributed across the posterior pole and are isolated or clustered in small groups.
- The deposits appear with irregular, complex shapes but have distinct borders.
- Another important distinguishing feature is that these drusenoid lesions are associated with the presence of thickened choroid.



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Pachychoroid Disease Spectrum (PDS)

- Choroidal vascular congestion/ attenuation
  - Thickened sclera
  - Lengthened intrascleral course of vortex veins
- Physiologic Factors
  - Excess choroidal interstitial fluid/choroidal vascular hyperpermeability (CVH)
  - Precapillary arteriolar hypertension
  - Altered intravascular osmolality (serum proteins (albumin))
  - Pharmacologic agents
    - Corticosteroids
    - Phosphodiesterase (PDE) inhibitors
  - Alterations in interstitial tissues in the choroid

B Brown R, Mohan S, Chhablani J. Pachychoroid Spectrum Disorders: An Updated Review. J Ophthalmic Vis Res. 2023 Apr 19;18(2):212-229.

Gallego-Pinazo R, et al. Med Hypothesis Discov Innov. 2014;3(4):111-116.

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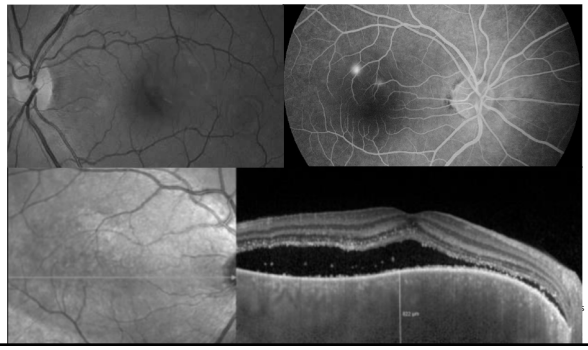

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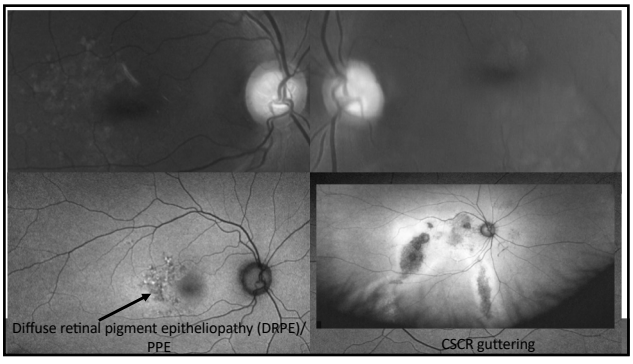

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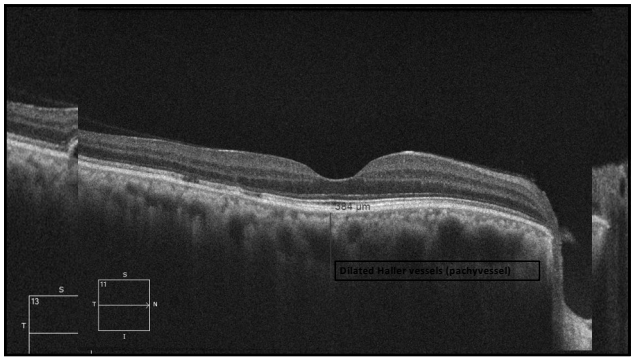

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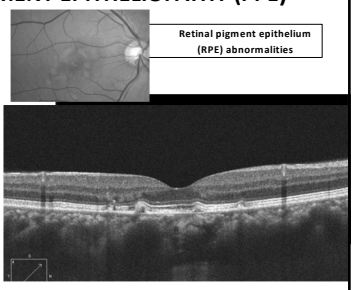
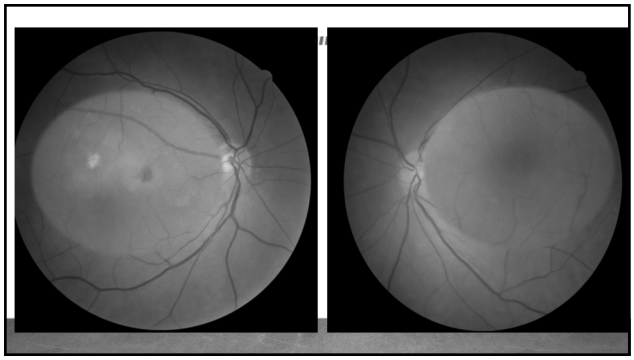
PACHYCHOROID PIGMENT EPITHELIOPATHY (PPE)

- Forme Fruste of CSC to Chronic CSC
- Orange red fundus appearance
- Absence of normal fundus tessellation
- RPE changes mistaken for ARMD or pattern dystrophy
- OCT scattered RPE elevations, small serous PEDs, thick choroid
- ICG shows mid-phase hyperfluorescence suggestive of hyperpermeability
- Fundus Autofluorescence shows granular hypoautofluorescence and stippled mixed areas of hyper and hypoFAF
- Management: Observation for progression to CSC, PVN, or even PCV



Gallego-Pinazo R, et al. Med Hypothesis Discov Innov. 2014;3(4):111-114

109



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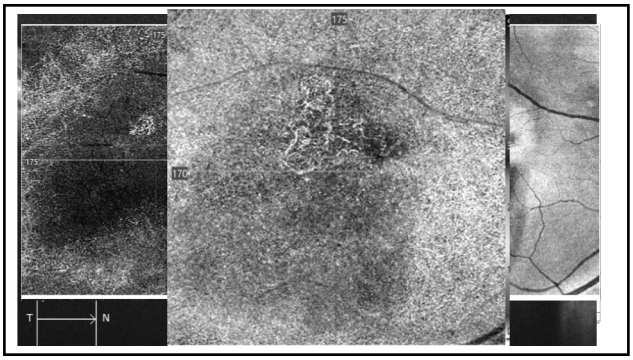

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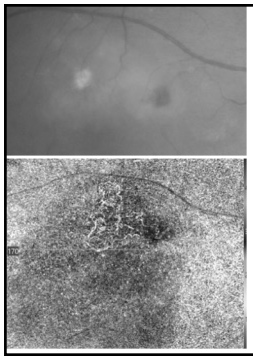

Pachychoroid Neovasculopathy (PNV)

- Characteristics:
  - OCT Findings of CSC and/or PPE
  - OCT (A)
    - Type 1 sub RPE CNV
    - With or without subretinal fluid
    - Double-layer Sign

Gallego-Pinazo R, et al. Med Hypothesis Discov Innov. 2014;3(4):111-114.

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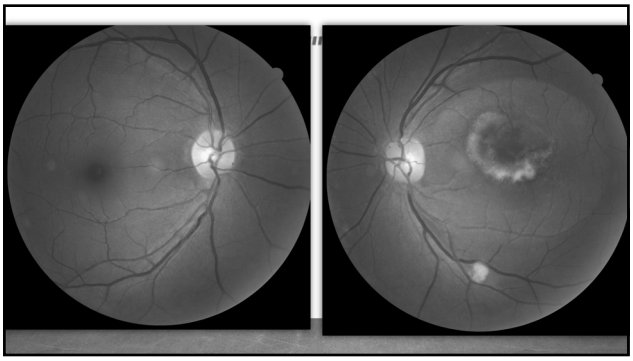

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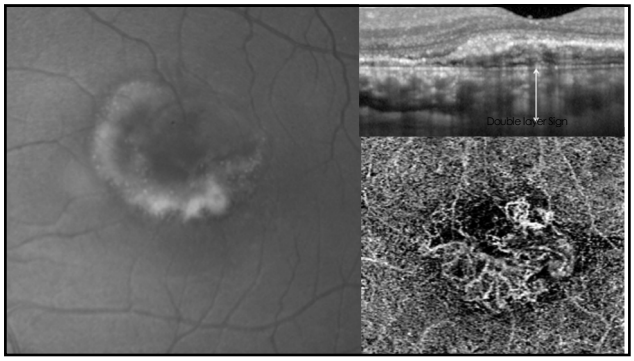

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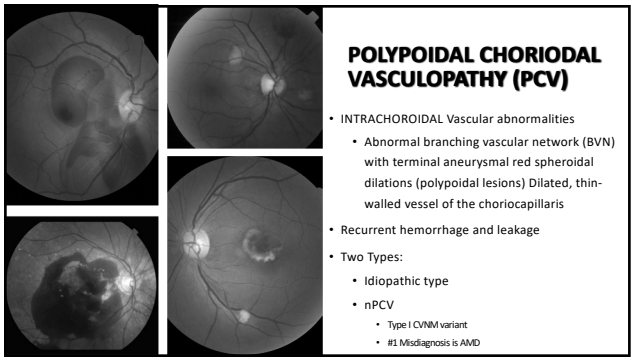

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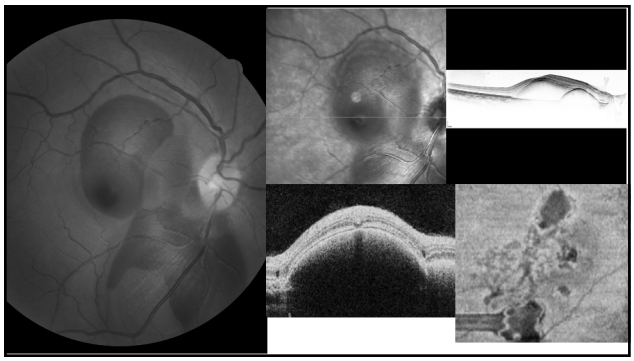

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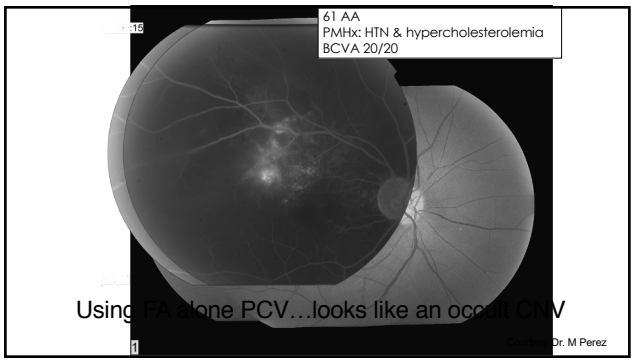

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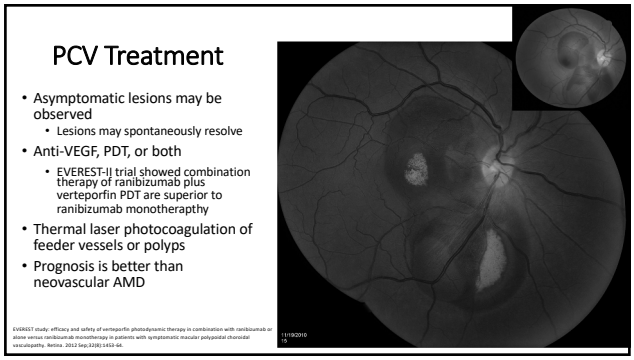

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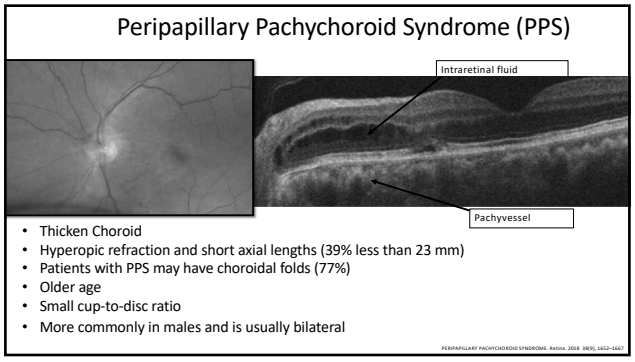

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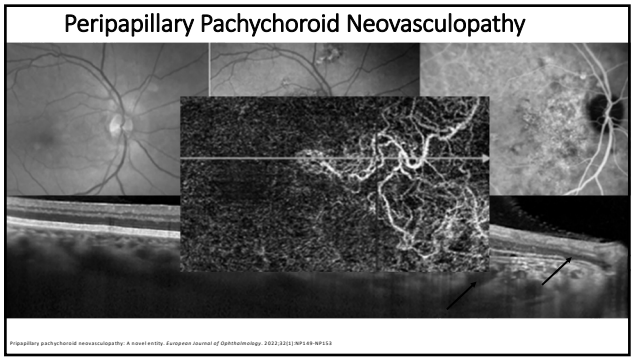

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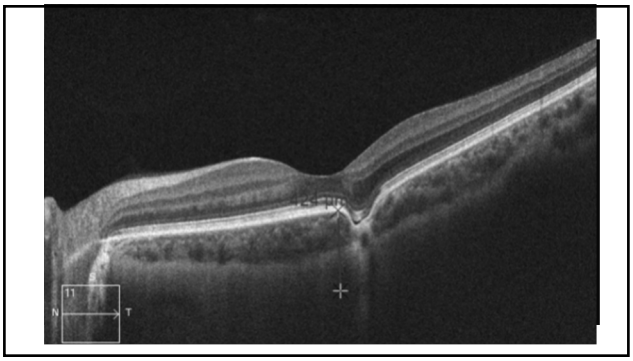

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Focal choroidal excavation (FCE)

FCE refers to a concavity of the choroid without local scleral changes

Often identified through a characteristic appearance on optical coherence tomography (OCT)

Unilaterally and is found incidentally on exam
Mostly diagnosed in fourth or fifth decade

FCE are thought to be congenital, however, the pathophysiology of FCE remains unclear.

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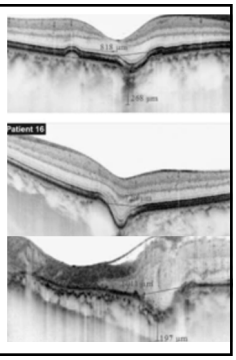
Focal Choroidal Excavation (FCE)

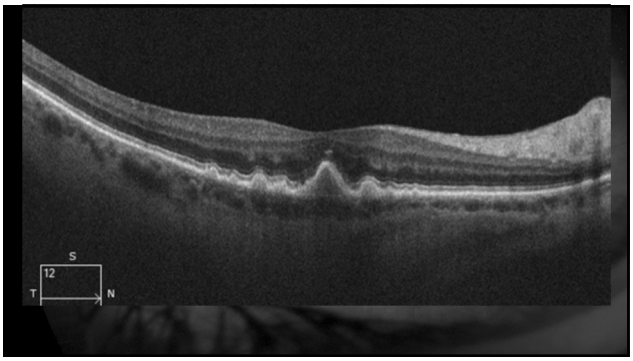
Three patterns

1. cone shaped—Most common pattern; all these cases had regular RPE on OCT and less degenerative changes on angiography, hence bearing a better prognosis.
2. Bowl shaped—Higher incidence of RPE disruptions on OCT and degenerative changes on angiography.
3. Mixed morphology—This pattern has features of both cone- and bowl-shaped FCEs.



Shinojima A , Kawamura A , Mori R , et al. Morphologic features of focal choroidal excavation on spectral domain optical coherence tomography with simultaneous angiography. Retina Phila Pa 2014;34:1407–14

123



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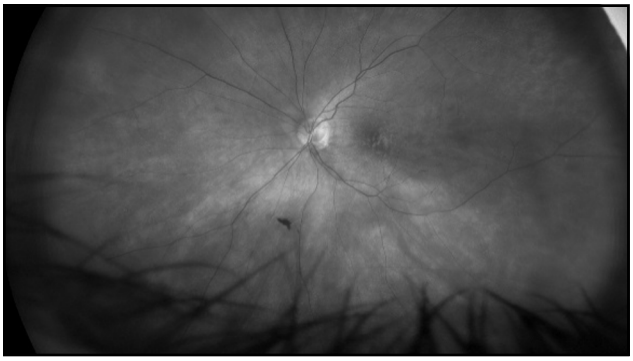

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Peripheral Exudative Hemorrhagic Chorioretinopathy (PEHCR)

First described by Annesley in 1980 as Peripheral Exudative hemorrhagic chorioretinopathy (PEHCR)

Bilateral

Predominantly affects older women

Signs include
Peripheral subretinal hemorrhage, subretinal fluid (SRF), exudation, and PED

Patients may be asymptomatic or have decreased visual acuity and flashes and floaters

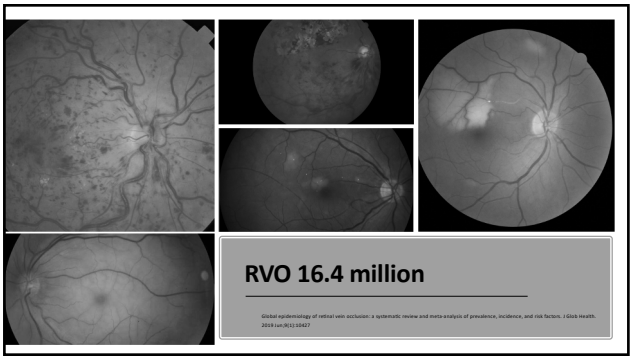
Has been postulated to be part of the Pachychoroid disease spectrum

One study found that the choroid in eyes with PEHCR is thickest in the temporal periphery

Club-shaped choroidal contour

Peripheral exudative hemorrhagic chorioretinopathy-A new addition to the spectrum of pachychoroid disease? Retina 2021;41:1518–1525.

126



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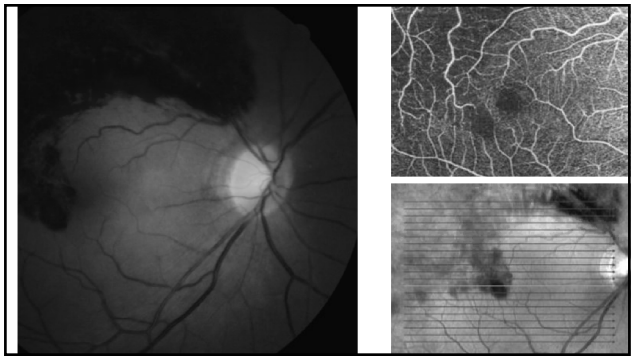

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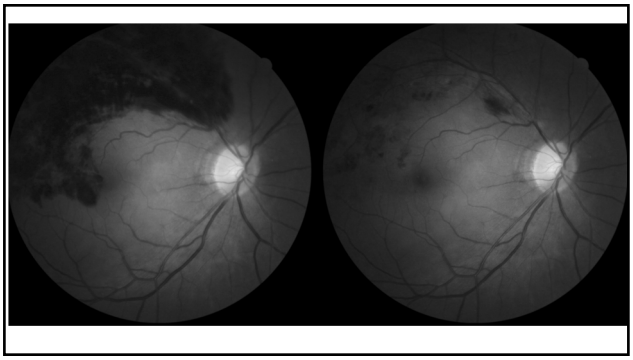

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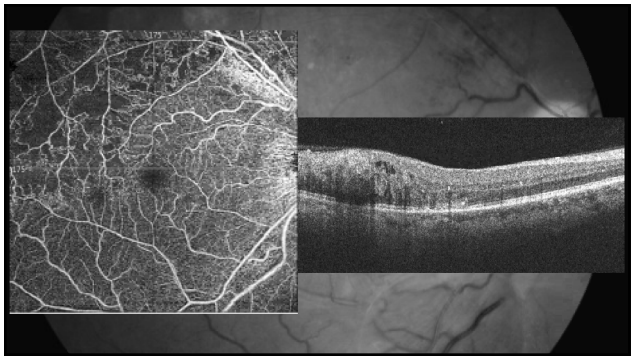

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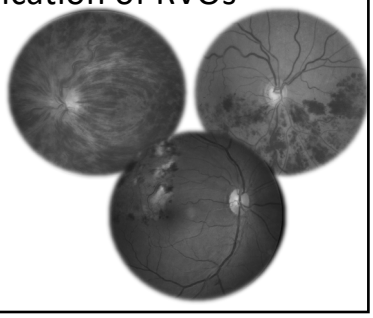
Classification of RVOs

- CRVO
  - Nonischemic CRVO
  - Ischemic CRVO
  - Juvenile CRVO
- HRVO
- BRVO
  - Major BRVO
  - Hemispheric BRVO
  - Macular BRVO
- RVO + any RAO



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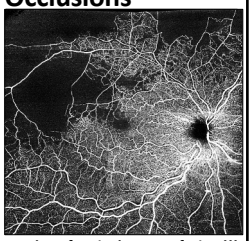
Branch Retinal Vein Occlusions

- Branch retinal vein occlusion (BRVO)
  - Occurs **4 to 6 times** more than its counterparts- (CRVO) or hemi-retinal vein occlusion (HRVO)
  - Up to 2/3 of BRVOs occur in the superior-temporal quadrant ~66%
- Hayreh classified BRVO into Two types:
  - ***Major BRVO (H*emispheric)**
  - when one of the major branch retinal veins is occluded
    - non-ischemic or ischemic
    - Ischemic BRVO is defined as > 5-disc diameters of nonperfusion on FA
  - ***Macular BRVO***, when one of the macular venules is occluded



Predictive Value of Retinal Non-perfusion !!!

BVOS 50/50/50 rule:

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

Branch retinal vein occlusion: natural history of visual outcome. JAMA Ophthalmol. 2014 Jan;132(1):13-22

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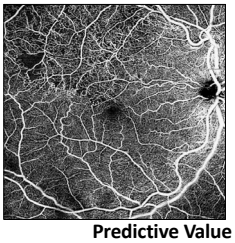
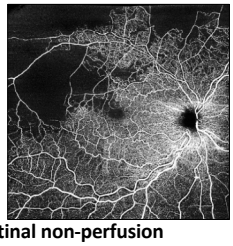
Non -ischemic BRVO



Ischemic BRVO



Predictive Value of Retinal non-perfusion

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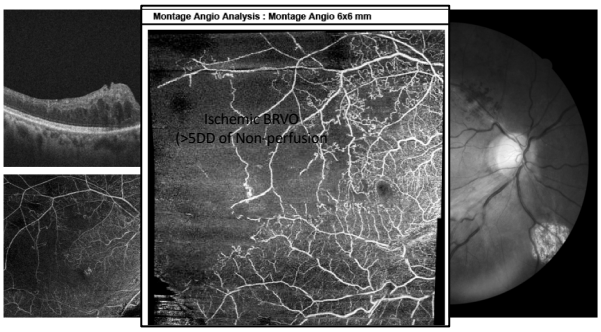
133



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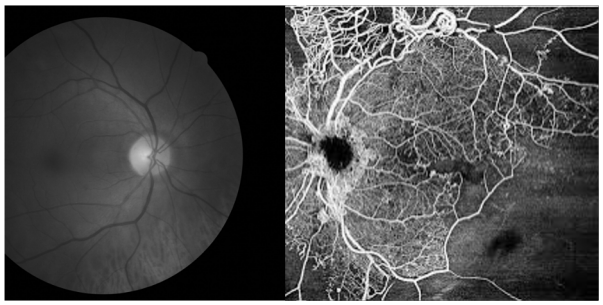
Ischemic CRVO



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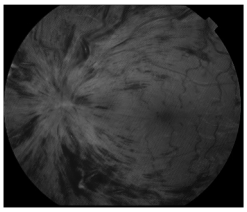
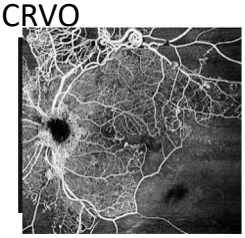
Ischemic CRVO





Widespread capillary non-perfusion

- Vision often < 20/200/ +APD/ Greater VF deficits
- Widespread capillary non-perfusion on FA **(> 10 DD)**
- NVG
  - As high as 60% vs 5% Nonischemic
  - "the three month glaucoma"
- <10% developed retinal neovascularization
  - Anterior segment

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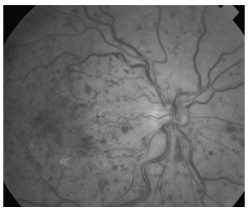
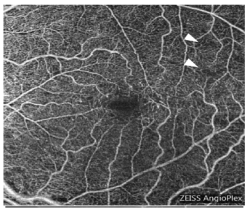
Non- Ischemic CRVO (75 %)





- Better vision and prognosis for spontaneous visual improvement
- 14% convert to ischemic within 4 months
  - The Central Vein Occlusion Study (CVOS) reported a conversion rate from nonischemic CRVO to ischemic CRVO of 3.3% by 4 months
- 1/3 with NVI / NVA

Natural history of central retinal vein occlusion: an evidence-based systematic review. Ophthalmology 2003;17:1083-1094

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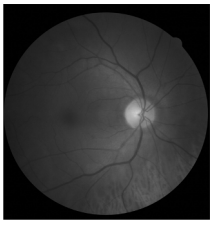
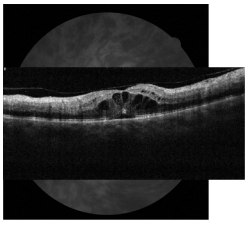
Juvenile CRVO





- Patients younger than 50 years of age
- Distinct clinical entity due to its more favorable prognosis
- Lower rate of ocular complications and positive response to periocular and intravitreal therapies.

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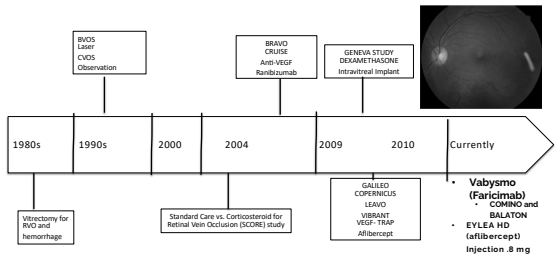
Retinal Vein Occlusion Intervention



Central Vein Occlusion Study Group. *Arch Ophthalmol*. 1997 Apr. 115(4):486-91.
Branch Vein Occlusion Study Group. *Arch Ophthalmol*. 1986;104(1):34-41.
The (SCORE) Study Report 5. Arch. Ophthalmol. 127, 1101–1114.
CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 117(6), 1124–1133

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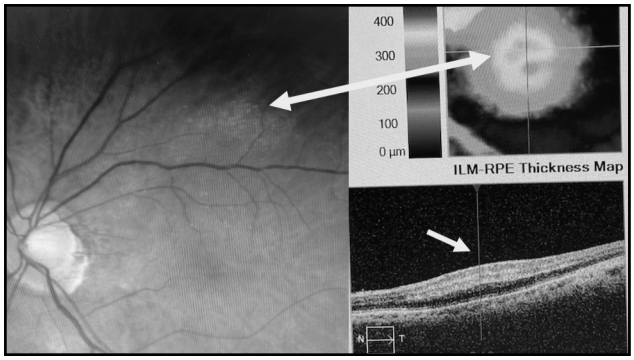

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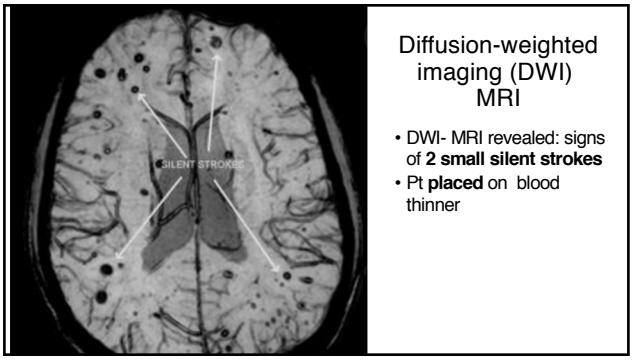

Diffusion-weighted imaging (DWI) MRI

- DWI- MRI revealed: signs of **2 small silent strokes**
- Pt **placed** on blood thinner

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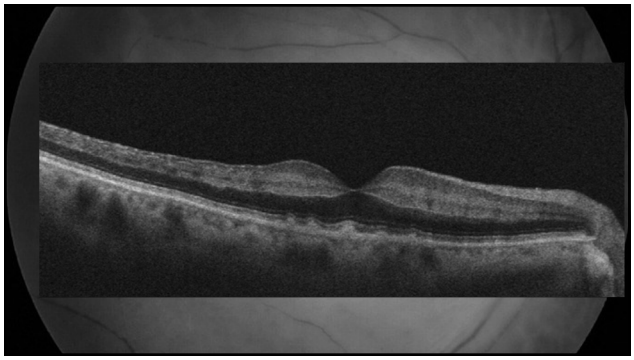

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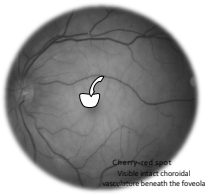
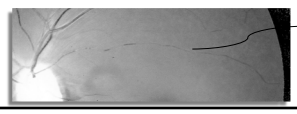
Central Artery Occlusion (CRAO)

- Characteristics
  - Sudden severe visual loss
  - Painless
  - Retinal appearance
    - Opaque and edematous
      - Most prominent in posterior pole
    - Thickest ganglion cell layer





Boxcarring- Retinal arterial attenuation with SEGEMENTED disruption of blood flow within an artery

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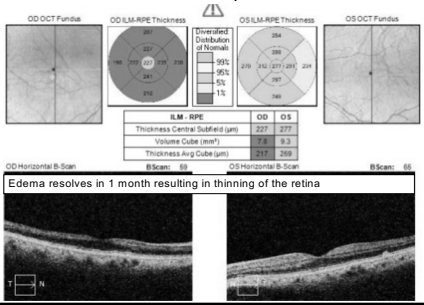
One month Follow-up



Edema resolves in 1 month resulting in thinning of the retina

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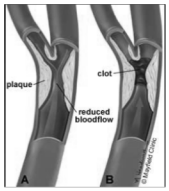
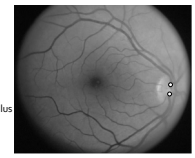
Pathogenesis of Retinal Artery Occlusion (RAO)



Atherosclerosis thrombosis at lamina cribosa

Emboli at CRA penetration site into optic nerve



- 30% patients had ICA stenosis (> 50%)
- 70% patients had ICA plaques
- 50% patients had abnormal echo with a source of embolus

Ophthalmology. 2009. 116:1928-36)

(Hayreh et al. Retinal artery occlusion. associated systemic and ophthalmic abnormalities. Ophthalmology. 2009. 116:1928-36)

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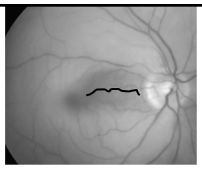
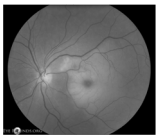
CRAO

- Non-Arteritic CRAO ~66.9%
  - 93.2% CF or worse, none better than 20/40
- Non-Arteritic CRAO w/ cilioretinal sparing~14.3%
  - 60% CF or worse, 20% better than 20/40
  - Patient cilioretinal artery improve visual prognosis
- Transient Non-Arteritic CRAO~ ~4.5%
  - CRA temporarily occluded
  - Fall in perfusion pressure, drop arterial BP or rise IOP, vasospasm
- Arteritic CRAO ~16%
  - Secondary to Giant Cell Arteritis (GCA)
  - Posterior ciliary artery and central retinal artery occlusion
  - Occult GCA – no systemic symptoms, always order labs to r/o





Hayreh et al. CRAO Visual Outcome. Am J Oph 2005

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Retinal Artery Occlusion Emergent Stroke Evaluation

CRAO, BRAO, & TIAs = a stroke & needs to be recognized as an EMERGENCY!

- Silent POSITIVE DWI-MRI strokes are seen in:
  - >55% of CRAO
  - ~31% of BRAO
  - ~18% OF TVO
- Pts with (+) DWR-MRI silent strokes have a High risk for MAJOR stroke
  - Especially during the next week to month
  - Rate for stroke peaks (~60%) within 1 week s/p RAO onset
- Urgent referral to ER (with stroke center) is CRUCIAL
  - Management requires identifying and treating risk factors + neuro consult + cardiology evaluation

Update on the Management of Central Retinal Artery Occlusion

Michael Dattilo, MD, MS[a,b,*], Valérie Biousse, MD[c,d,e,*], Nancy J. Newman, MD[c,d,e,*]

KEYWORDS
• Central retinal artery occlusion • Branch retinal artery occlusion • Stroke • Ischemia • Management • Treatment • Thrombolysis

KEY POINTS
- Acute central retinal artery occlusion (CRAO) and branch retinal artery occlusion (BRAO) are the ocular equivalent of a cerebral infarction in the anterior circulation.
- The risk factors for a CRAO or a BRAO and acute cerebral ischemia are very similar.
- Patients with acute CRAO and BRAO need to be evaluated emergently in a stroke center similar to patients with acute cerebral ischemia.
- Up to 24% of patients with acute retinal ischemia have concomitant cerebral infarctions on brain diffusion-weighted MRI.
- Because no current therapeutic intervention has been shown to improve visual outcome compared with the natural history of CRAO, management of CRAO should be focused on secondary prevention of vascular events, such as cerebral ischemia, myocardial infarction, and cardiovascular death.

Retinal and ophthalmic artery occlusions preferred practice pattern [published correction appears in *Ophthalmology*. 2020;127(9):1280]. *Ophthalmology*. 2020;127(2):P259-P287.
Bulwa ZB, Mendelson SJ, Bronson JR. Acute secondary prevention of ischemic stroke: overlooked no longer. Front Neurol. 2021;12:701168.

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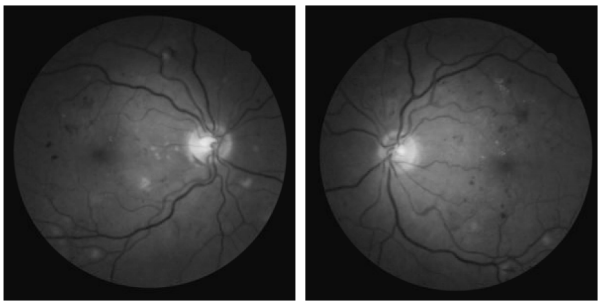

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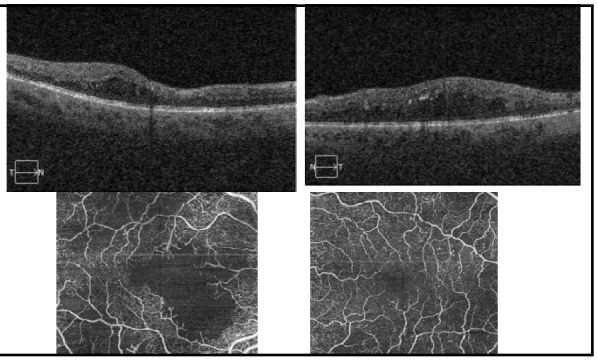

149

Diabetic Retinopathy is the 1st cause of Vision Loss in Adults Aged 20–74 years old

Diabetes In the United States
38.4 million
Diagnosed: 29.7
Undiagnosed: 8.7 million
Prediabetes: 96 million

537 million adults have diabetes
> 1.31 Billion people could be living with diabetes by 2050

…these numbers are expected to rise as the prevalence of diabetes increases

Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html Accessed March, 2024 2American Diabetes Association. Diabetes Care 2023;46(Supplement_1):S203–S215
International Diabetes Federation Atlas 10th edition.
Available from https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html; Accessed 9 October 2023

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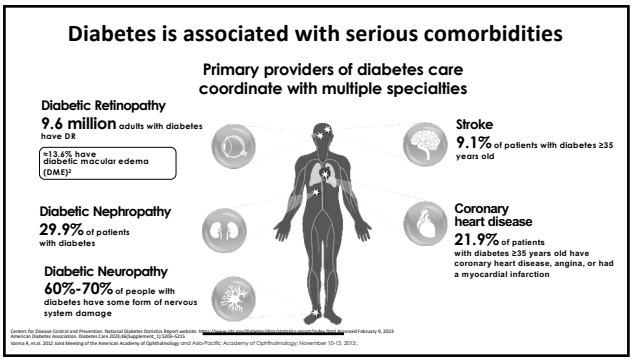

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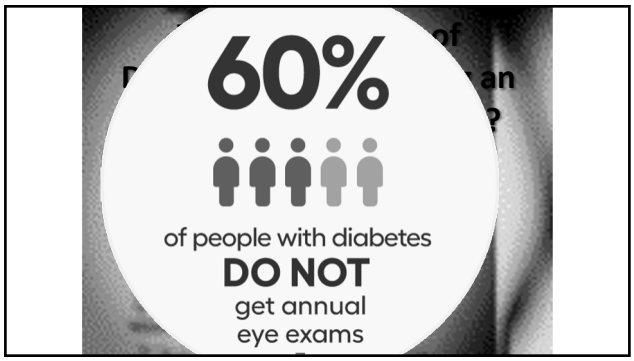

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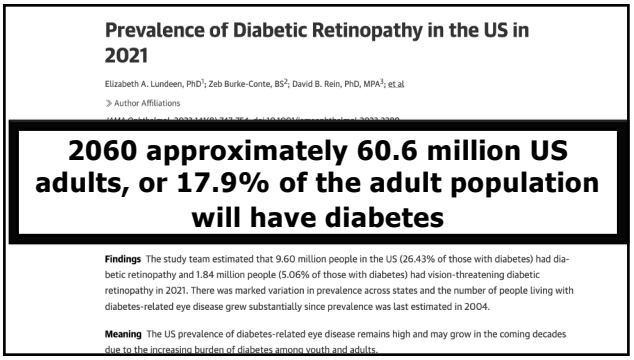

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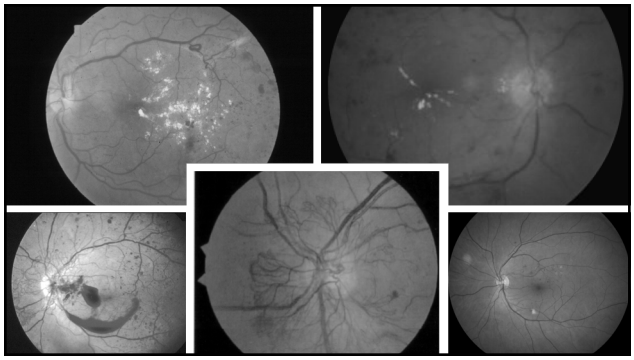

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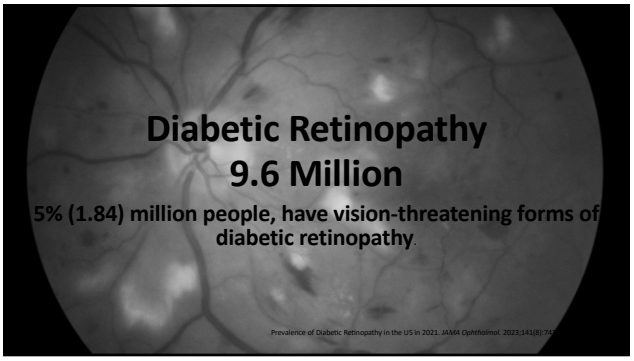

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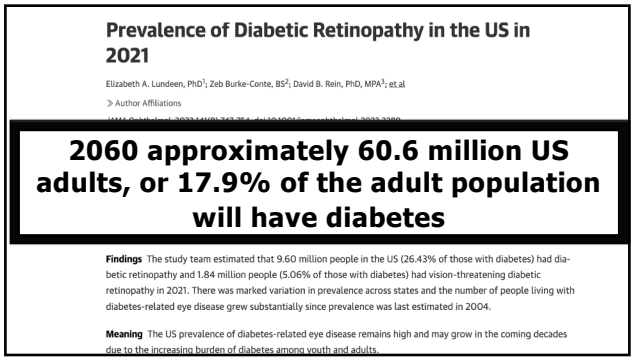

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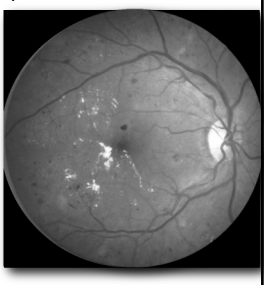
Diabetic Retinopathy

- Classification of Diabetic Retinopathy
  - Non-proliferative DR
    - Mild- Microaneurysms (MAs) only
    - Moderate
      - Hemorrhages, exudates and/or microaneurysms
      - Cotton wool spot (CWS)
      - Venous beading (VB) or intraretinal microvascular abnormalities (IRMA)
    - Severe
    - Very Severe (4-2-1)
      - Severe findings without neovascularization
      - >50% will progress to proliferative DR in one year



Adapted with permission from Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1679.

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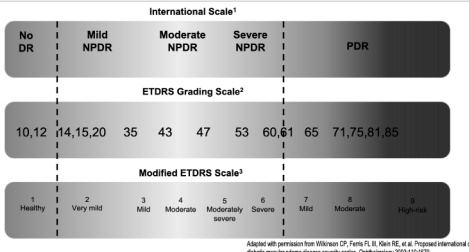
DIABETIC RETINOPATHY SEVERITY SCALES



Adapted with permission from Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1679.
ETDRS Report Number 10. Ophthalmology. 1991 May;98 (5):786- 806

The Diabetic Retinopathy Study Research Group. A Modification of the Airlie House Classification of Diabetic

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Disease Severity	Definition	Management	Natural History
No retinopathy	Diabetic retinopathy absent	12 months	
Mild NPDR	MAs only	12 months	***5% risk of progression to proliferative diabetic retinopathy (PDR) within one year.**
Moderate NPDR	MAs plus, exudates, cotton wool spots, retinal hemorrhages, intraretinal microvascular abnormality, venous beading	Three to six months *Depends on severity of signs, stability, systemic factors, and patient's glycemic control	***Up to 27 % risk of progression to proliferative diabetic retinopathy (PDR) within one ye ar.**
Severe NPDER (4-2-1) rule	Severe retinal hemorrhages in four quadrants, or venous beading in at least two quadrants, or moderately severe intraretinal microvascular abnormality in at least one quadrant	Two to three months	***Proliferative diabetic retinopathy in up to 50% within a year**

American Optometric Association. Evidence-based Clinical Practice Guideline: Eye Care of the Patient With Diabetes Mellitus. www.aoa.org/optometrists/tools-and-resources/evidence-based-optometry/evidence-based-clinical-practice-guidlines/cpg-3--eye-care-of-the-patient-with-diabetes-mellitus. Accessed October 8, 2023

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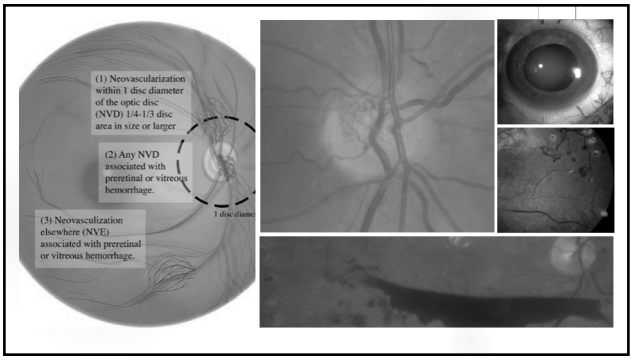

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Proliferative Diabetic Retinopathy

PDR	**Neovascularization Vitreous Hemorrhage**		**Retina referral within one week**
	High Risk: **1. NVD > 1/4-to-1/3-disc area** **2. Any NVD associated with vitreous or preretinal hemorrhage** **3. Any NVE associated with vitreous or preretinal hemorrhage**		**Retina referral within one day to two days**

American Optometric Association. Evidence-based Clinical Practice Guideline: Eye Care of the Patient With Diabetes Mellitus. www.aoa.org/optometrists/tools-and-resources/evidence-based-optometry/evidence-based-clinical-practice-guidlines/cpg-3--eye-care-of-the-patient-with-diabetes-mellitus. Accessed October 8, 2023

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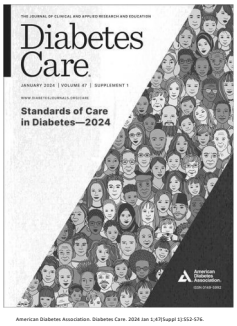

American Diabetes Association. Diabetes Care. 2024 Jan 1;47(Suppl 1):S1-S4.

New in 2024

- HbA1c near normal 6%
- CGM in patients on Insulin
  - Time in Range (TIR)
  - Target range: 70–180 mg/dL
  - Recommended TIR for most: >70%
- Stricter BP targets (≤130/80)
- New lipid management recommendations- LDL <70 mg/dL in general and <55 mg/dL for those with preexisting atherosclerotic CVD
- Higher weight loss targets (up to 15%) based on the efficacy of and access to newer medications such as high-dose semaglutide and tirzepatide
- Screen for Sleep Apnea
- Social Determinant of Health (SDOH)

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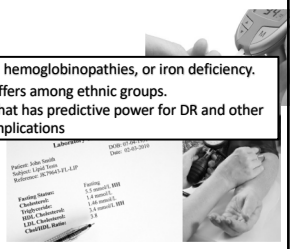
Risk Factors for Retinopathy

- **Duration /severity**
  - ≥10 years: 8.5 times more likely to have DR/DME

*A1C is unreliable in patients with anemia, hemoglobinopathies, or iron deficiency.
*Evidence shows that A1C differs among ethnic groups.
*HbA1c does not reveal glucose variability that has predictive power for DR and other diabetes complications

- **Hyperlipidemia**
- **Overweight / obesity**
- **Pregnancy**
- **Smoking**



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Continuous glucose monitoring (cgm)

- Sensor measures interstitial glucose levels continuously throughout the day.
- Wirelessly sends glycemic data to a monitor or smartphone app.
- May be connected to an insulin delivery system (hybrid closed-loop system, automating basal insulin delivery).
- Standardized reports allow patients and providers to identify glycemic trends and easily review the percentage of time spent above, in, or below a target glycemic range.

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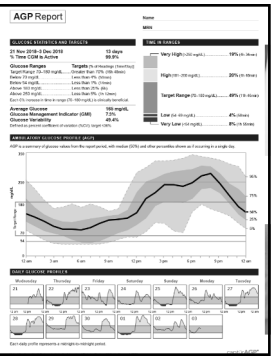
Time in Range (TIR)

- A new parameter to evaluate blood glucose control
- Indicates the percentage time a person's glucose value was within the target range during a defined period
- Target range: **70–180 mg/dL**
- Recommended TIR for most: **>70%**
- **The higher the TIR range percentage- the lower the risk of developing complications**
- **The lower the TIR range percentage, the higher the risk of developing complications**

American Diabetes Association. Diabetes Care 2023;46(Supplement_1):S203–S215
American Diabetes Association. Diabetes Care. 2024 Jan 1;47(Suppl 1):S52-S76.



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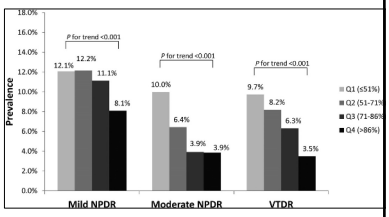
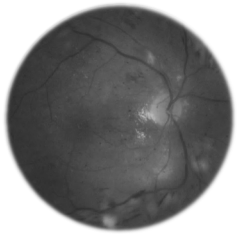
Time in range (TIR) and Complications

- The higher the TIR range percentage- the lower the risk of developing complications
- The lower the TIR range percentage, the higher the risk of developing complications
- Lu et al., 2018: patients with more advanced DR had significantly less TIR and higher measures of glycemic variability than those with less severe or no DR. TIR was significantly associated with prevalence of all stages of DR.

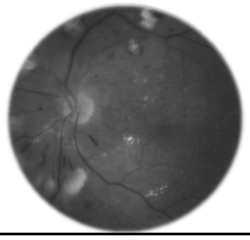


NPDR, nonproliferative diabetic retinopathy; VTDR, vision-threatening diabetic retinopathy.

166



64 yo BM
Diabetes X 10 years



Avg BSL 330
BP 190/100

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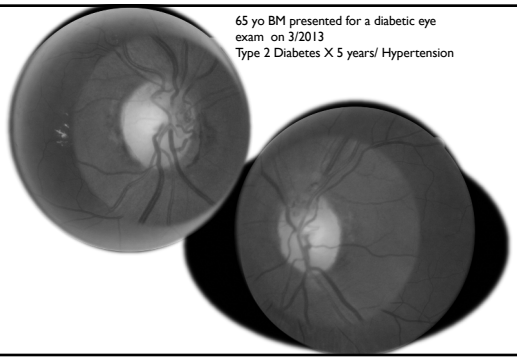

65 yo BM presented for a diabetic eye exam on 3/2013
Type 2 Diabetes X 5 years/ Hypertension

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- **Wegovy, Ozempic: Once a Week Injections-Potent Weight Loss Meds**
- Ozempic: Semaglutides (0.5mg, 1 mg or 2mg)
- Glucagon-like peptide 1 receptor agonists (GLP-1 RA)
- Promotes the pancreas to release insulin
  - only when glucose values are elevated
  - makes people feel fuller faster so they tend to eat less,
  - Reduces the amount of glucose made by the liver.
- 25% weight loss from baseline
- Wegovy- higher dose (2.4mg)

- **Mounjaro (tirzepatide) injection**
- Activates both the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor
- 5milligrams, 10 milligrams and 15 milligrams
- Average Weight Loss of 60 Pounds Reported
- 10/2023- FDA Approved

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Complications

Pancreatitis-Inflammation of the pancreas	Low blood sugar (hypoglycemia)
Serious allergic reactions	Kidney problems (kidney failure)
Severe stomach problems (stomach paralysis)	Gallbladder problems

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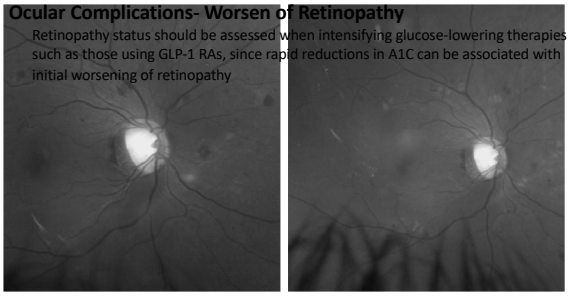
Ocular Complications- Worsen of Retinopathy

Retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RAs, since rapid reductions in A1C can be associated with initial worsening of retinopathy



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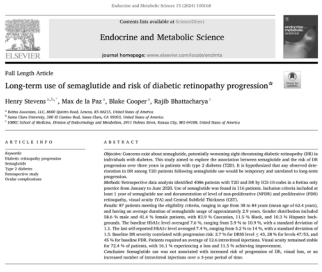

Endocrine and Metabolic Science

Full Length Article

Long-term use of semaglutide and risk of diabetic retinopathy progression*

Henry Stevens, Max de la Paz, Blake Cooper, Rajib Bhattacharya

Highlights

- Of the 87 patients (174 eyes), 14.4 % had severe NPDR at the outset.
- The progression rate to PDR for those with severe NPDR over a year historically is 50 %.
- 3-Year progression rate to PDR for those with severe NPDR on semaglutide was 28 %.
- 63.2 % of patients required intravitreal injections, averaging 6.1 injections per patient.
- Visual acuity over 3 years: 72.4 % stable, 16.1 % loss, and 11.5 % gain

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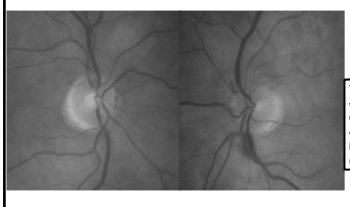
Ocular complications

- **Non-arteritic anterior ischemic optic neuropathy (NAION)**



July 3, 2024

Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide

The cumulative incidence of NAION for the semaglutide vs non–GLP-1 RA cohorts over 36 months was 6.7% (95% CI, 3.6%-9.7%) and 0.8% (95% CI, 0%-1.8%), respectively. A Cox proportional hazards regression model showed a higher risk of NAION for patients prescribed semaglutide (HR, 7.64; 95% CI, 2.21-26.36; $P < .001$).

Molteo SP. Semaglutide and Nonarteritic Anterior Ischemic Optic Neuropathy. JAMA Ophthalmol. Published online July 03, 2024. doi:10.1001/jamaophthalmol.2024.2514

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Social Determinants Of Health Affect the Patient Care Journey and Can Drive A Majority Of Overall Patient Outcomes

Patient Outcomes Drivers

80% Social Determinants

20% Medical Care

Factors that contribute to underutilization of care

- Trust
- Patient-provider communication
- Fear of medical or surgical treatment
- Transportation issues
- Lack of insurance/cost
- Other health problems
- Poor social support structure
- Cultural and language barriers
- Lower literacy level
- Immigration status
- Provider accessibility

Despite being at risk for higher visual impairment and blindness, Black and **Hispanic/Latino patients are less likely than White patients to be seen by an ophthalmologist or have a dilated exam.**

L Hood CM et al. Am J Prev Med. 2016;50(1):129-135. doi:10.1016/j.amepre.2015.08.024 2. Office of Disease Prevention and Health Promotion. Accessed April 19, 2023. https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health

175

- Eyes with predominantly peripheral lesions- PPLs (defined as outside of ETDRS 7 standard field) had a 4.7-fold increased risk of progression to proliferative diabetic retinopathy (PDR) over 4 years.

Ophthalmology. 2015 May;122(5):949-56.

- Diabetic Retinopathy Clinical Research Retina Network (DRCR.net) Protocol AA- peripheral lesions (PPL) using ultra-widefield (UWF) color retinal imaging were not predictive of significant, 2-step worsening on the Diabetic Retinopathy Severity Scale (DRSS)
- FA-PPL but not color-image PPL have predictive value for NPDR progression and should be included in future DR studies.

JAMA Ophthalmol. 2022;140(10):946-954. Published correction in JAMA Ophthalmol. Published online November 17, 2022.

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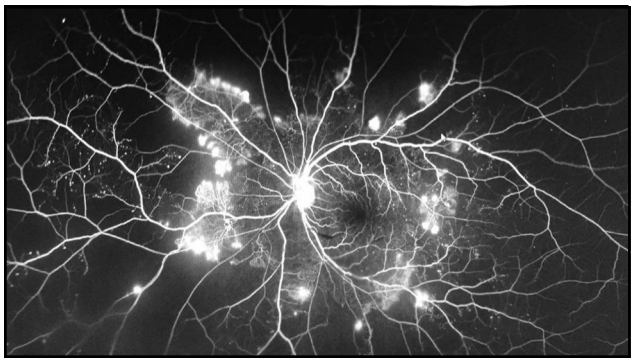

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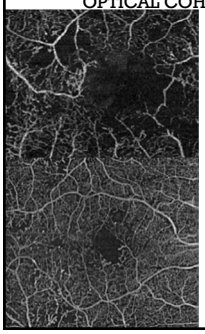
OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY (OCTA)



Diabetic Retinopathy

- Vascular anomalies (loops & dilations)
- Microaneurysms (MAs)
- Neovascularization
- Capillary dropout & FAZ enlargement

- Evaluation of subclinical DR may change follow-up or how the PCP manage the patient
- Color code points to area of abnormality
- Microaneurysms are green because they are in DEEP layer

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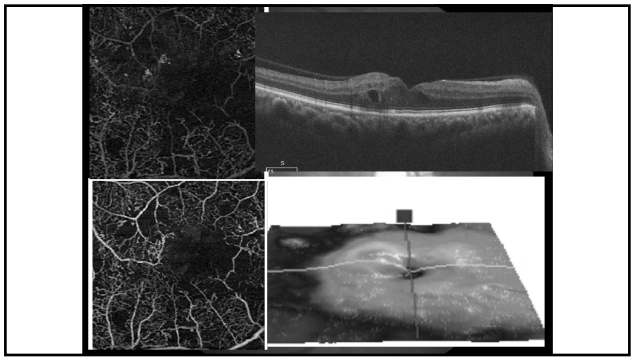

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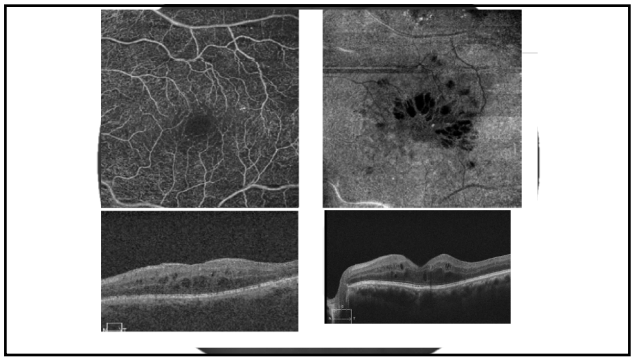

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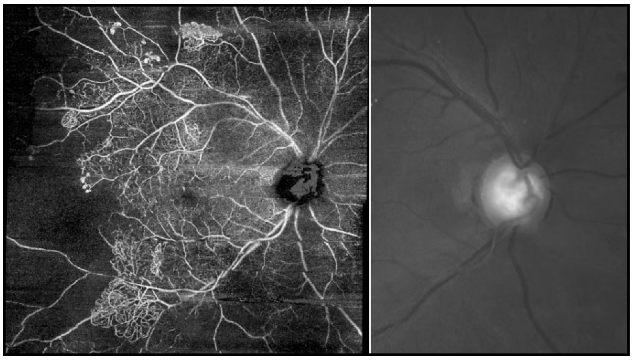

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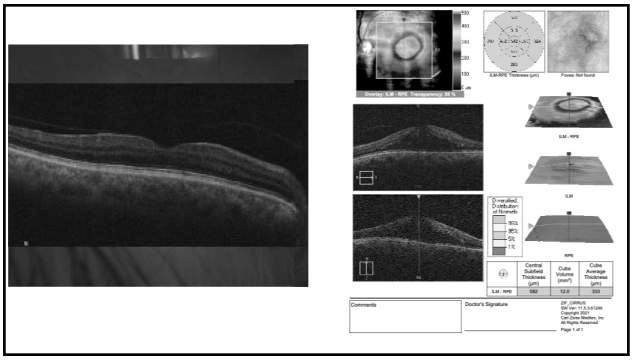

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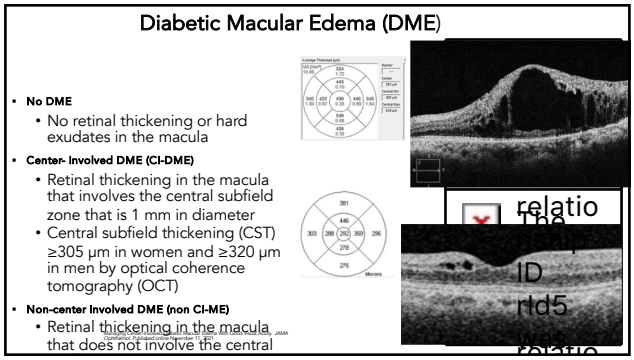

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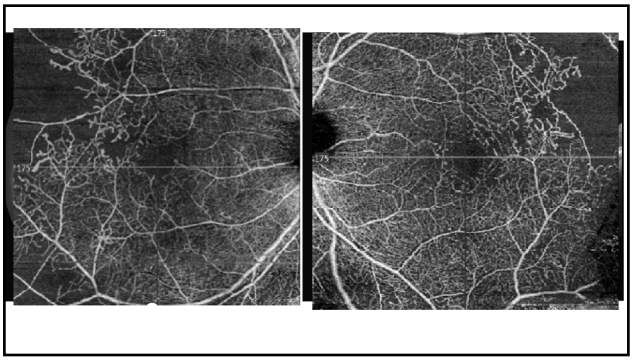

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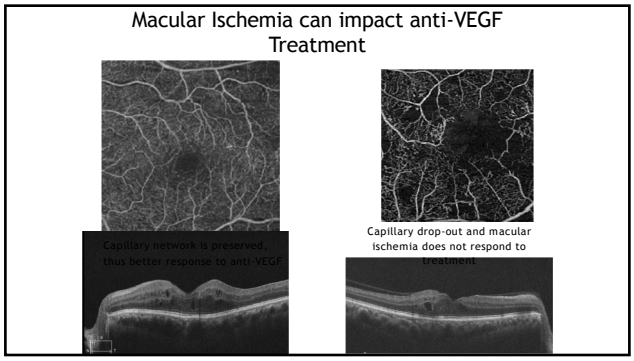

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Approved Agents for DR/DME

Ranibizumab 0.3 mg (DME)

Aflibercept 2.0 mg

Brolucizumab 6.0 mg

Faricimab 6.0 mg

Aflibercept HD (8.0 mg)

Steroids:
Dexamethasone implant (Ozurdex)
Fluocinolone implant (Iluvien)
Intravitreal Triamcinolone (Triessence)

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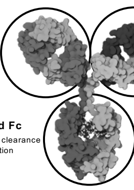
Vabysmo: First Bispecific Antibody Designed for Intravitreal Use

Engineered for efficacy, duration within the eye, and fast systemic clearance

1 molecule, 2 targets

Anti–Ang-2 Fab
- Enhanced activity through Ang-2 inhibition



Anti–VEGF-A Fab
- Proven efficacy through VEGF-A inhibition

Optimized Fc
- Faster systemic clearance
- No effector function

Regula JT, et al. EMBO Mol Med 2016;8:1265-1288. Regula JT et al. EMBO Mol Med. 2019;11(5):e10666.
Ang-2, angiopoietin-2; Fab, fragment antigen binding; Fc, fragment crystallizable; VEGF-A, vascular endothelial growth factor-A.

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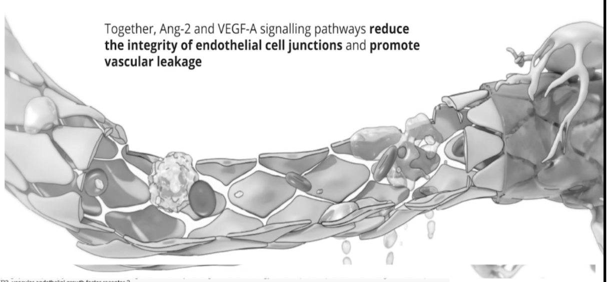
Under Physiological Conditions, the Angiopoietin Pathway Maintains Vascular Stability and Homeostasis[1-3]



VEGFR2, vascular endothelial growth factor receptor-2.

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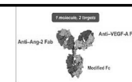
Vabysmo (faricimab)



- Roche/Genentech
  - FDA approved January 3, 2022 for AMD and DME
- First bi-specific antibody for intraocular use
  - One arm: Vegf-A inhibitor
  - Other arm: Angiopoietin-2 (Ang-2)inhibitor
    - growth factor that promotes vascular destabilization and and inflammation
  - Dual inhibition of VEGF and Ang-2 have proven more effective than inhibiting either target alone
- Multiple studies show similar results to monthly Lucentis/Eylea but able to object less frequently, many patients q 16 weeks
- October 2023- FDA approved for RVO
  - COMINO and BALATON

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Elevatum Study Design and Rationale: Phase 4 Trial of Faricimab (Vabysmo) in Underrepresented Patients With Diabetic Macular Edema

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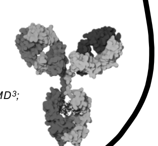

Presented at the American Society of Retina Specialists Annual Meeting
Seattle, WA | July 27–August 1, 2023

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Racial and Ethnic Disparity in the Prevalence of Diabetes and Diabetic Retinopathy/Diabetic Macular Edema

Underrepresented populations are **more affected** by diabetes and **diabetic eye diseases**[1,2]

- Prevalence of diabetic retinopathy is **33.4% in Hispanic** patients and **26.5% in Black** patients **vs 18.2% in White** patients[3]
- **Hispanic and Black** patients have **worse baseline VA** and **disease severity** on starting anti-VEGF therapy for DME vs **White** patients[4]

A retrospective study showed that **VA improvements** following 1 anti-VEGF injection were **lowest** in **Black (26.7%) and Hispanic (39.4%)** patients with DME compared with **White (50.0%)** patients with DME[5]

Minority populations are **largely underrepresented in clinical trials** that have led to FDA-approved ophthalmology therapies[6]

The **aim** of **Elevatum** is to **evaluate** the treatment response and safety of **faricimab** in traditionally **underrepresented**, treatment-naïve patients with DME

DME, diabetic macular edema; FDA, US Food and Drug Administration; VA, visual acuity; VEGF, vascular endothelial growth factor.

1. Centers for Disease Control and Prevention. *National Diabetes Statistics Report*, 2020. Accessed March 2022. https://www.cdc.gov/diabetes/data/statistics-report/diagnosed-diabetes.html; 2. Zhang X et al. *JAMA.* 2010;304:649-656. 3. Spanakis EK, Golden SH. *Curr Diab Rep.* 2013;13(6):814-823. doi:10.1007/s11892-013-0421-9; 4. Malhotra N et al. *Am J Ophthalmol.* 2021;128:1438-1447. 5. Osathanugrah P et al. *Am J Ophthalmol.* 2021;222:310-317. 6. Sanjiv N et al. *JNMA.* 2022:18:56.

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High Dose Aflibercept (Eylea)

- PULSAR (AMD) and PHOTON (DME) Studies
  - Looked at 8 mg vs 2 mg of Eylea
  - Demonstrated non-inferior and clinically equivalent vision gains at 48 weeks with 8 mg at 12- and 16-week dosing after 3 initial doses compared to Eylea every 8 weeks after initial dosing
- Eylea HD FDA approved 8/18/2023 for AMD, DME and DR
  - 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

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Treatment for Central-involved DME in Eyes with Very Good Visual Acuity (DRCR.net Protocol V)

- 702 randomized participants completed two-year follow-up
- What is the best *treatment strategy* for eyes with central-involved (CI) DME and good visual acuity?
  - » For eyes with center-involving DME and visual acuity of 20/25 or better, observation with close follow-up may be a reasonable initial management option and doesn't compromise visual acuity outcomes at two years.
  - » Close follow-up is important, as patients were followed every eight to 16 weeks and rescued with aflibercept if their vision declined.
- DME can be clinically sub-divided into three relevant categories
  - CI-DME with VA impairment
  - CI-DME with good VA
  - Non-CI-DME.[1]

Baker SJ, Wolfe JD, Regillo CD, et al. Evidence-Based Guidelines for Management of Diabetic Macular Edema. Journal of VitreoRetinal Diseases. 2016.

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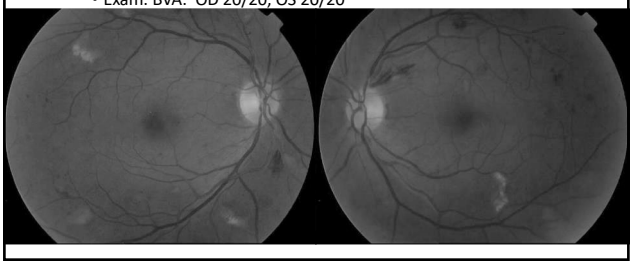
- 50-year-old male c/o blurry vision OU. Had refraction 9 months ago
- LPE: 20 years ago claims to be in good health
- Exam: BVA: OD 20/20, OS 20/20

Would patients with severe NPDR benefit from Anti-VEGF Treatment?



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Panorama Study

- Enrolled eyes with moderate-to-severe and severe nonproliferative diabetic retinopathy (NPDR) with or without DME
- Showed that eyes treated with aflibercept (Eylea, Regeneron) had significantly greater improvement of 2 or more steps in DR severity compared with the sham group.
- As a secondary outcome, the study demonstrated that the anti-VEGF treatment reduced the likelihood of developing vision-threatening complications such as center-involved DME (CI-DME) or PDR.

DRCR.net Protocol W

- Protocol W is a prospective multicenter study by the DRCR Retina Network that included eyes with moderate-to-severe NPDR and without baseline CI-DME
- The study was designed as a long-term evaluation of intravitreal aflibercept's ability to prevent PDR and CI-DME in eyes with advanced DR.
- Two-year result summary result - Preventive treatment with aflibercept resulted in a threefold reduction in the development of CI-DME with vision loss (14.8% in the sham group vs 4.1% in the aflibercept group).
- Treatment was also associated with a nearly twofold reduction in the development of new-onset PDR (33.2% in the sham group vs 13.5% in the aflibercept group)

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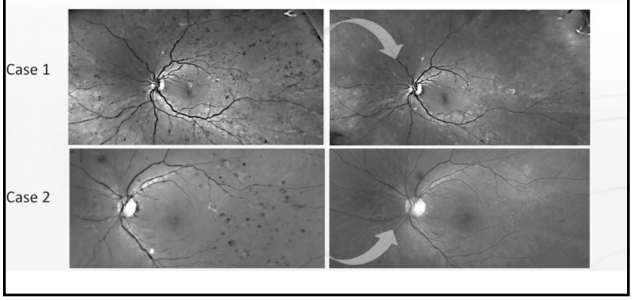
Anti-VEGF Improves NPDR



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Original Investigation

February 7, 2023

Four-Year Visual Outcomes in the Protocol W Randomized Trial of Intravitreous Aflibercept for Prevention of Vision-Threatening Complications of Diabetic Retinopathy

Raj K. Maturi, MD[1,2]; Adam R. Glassman, MS[3]; Kristin Josic, PHD[3]; et al

» Author Affiliations

JAMA. 2023;329(5):376-385. doi:10.1001/jama.2022.25029

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Key Points
Question In patients with nonproliferative diabetic retinopathy (NPDR) and good vision but without center-involved diabetic macular edema (CI-DME), does early aflibercept reduce disease progression and improve long-term visual acuity compared with initial observation and treatment only if disease worsens?
Findings This study presents 4-year primary outcomes of a randomized clinical trial that included 328 patients (399 eyes), randomized to 2.0 mg aflibercept injections or sham injections. Among those receiving aflibercept, proliferative diabetic retinopathy or CI-DME developed in 33.9% vs 56.9% among those who received sham—a difference that was statistically significant. Change in visual acuity was −2.7 vs −2.4 letters, a difference that was not statistically significant.
Meaning At 4 years, treatment of NPDR with aflibercept vs sham treatment resulted in statistically significant anatomic improvement, but no improvement in visual acuity.

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Agents for DR/DME

Biosimilars-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."
Ocuphire Pharma's APX3330-A twice-daily oral tablet
Ocuterra-Topical Administration of anti-VEGF agent in eye drop form (OTT-166) Failed Phase 2 (3/2024)

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Ocuterra

- Topical Administration of anti-VEGF agent in eye drop form (OTT-166)

BIOTECH

Phase 2 fail sends OcuTerra's eye drop dreams down the drain

By **Gabrielle Masson** · Mar 14, 2024 9:15am

- Secondary endpoints:
  - Prevention of progression to VTC
  - Delay in time to PRP or intravitreal injection

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Ocuphire Pharma's APX3330

- A twice-daily oral tablet

Ocuphire Pharma Announces Successful End-of-Phase 2 Meeting with FDA for Oral APX3330 in Diabetic Retinopathy

November 02, 2023 Download as PDF

- Participants received either APX3330 60U mg per day or a placebo. The primary endpoint was the percentage of participants with a 2-step or greater improvement in the Diabetic Retinopathy Severity Scale (DRSS) by week 24.
- Moderately severe to severe NPDR and mild PDR

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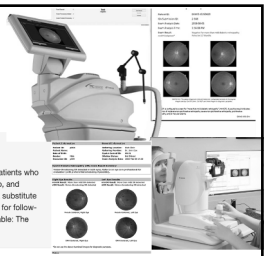
ARTIFICIAL INTELLIGENCE for the Screening of Diabetic Retinopathy



TELEMEDICINE AND ARTIFICIAL INTELLIGENCE FOR DIABETES

The American Diabetes Association (ADA) recommends retinal telemedicine screening to identify patients who have DR as a method of overcoming barriers to in-person care, such as a low provider-to-patient ratio, and prohibitive distance to reach a provider.[23] That said, it's important to note that retinal photos are not a substitute for a comprehensive dilated eye exam. This is especially the case when the photos are unreliable and for follow-up if abnormalities are detected. Two automated deep-learning artificial intelligence devices are available: The IDx-DR, from Digital Diagnostics, and the EyeScreen, from Eyenuk, Inc.

- The Dx-DR sensitivity and specificity of 87.4% and 89.5%, respectively, 1 in 10 patients will have a false-positive or false-negative result.
- EyeNuk is an AI screening program that utilizes the EyeArt software which has shown positive results with over 95% sensitivity when using fundus images obtained from smartphone

US Food and Drug Administration. FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems. 2018. Accessed August 27, 2022.

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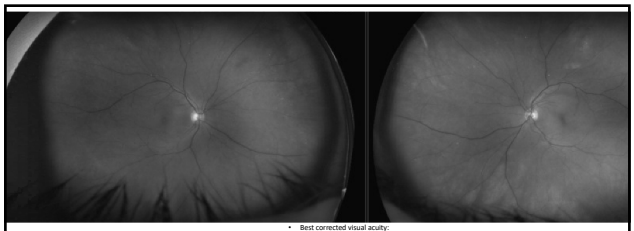

78-yo White Female s/p CE

- Best corrected visual acuity:
  - OD 20/50 NIPH
  - OS 20/20
- Extraocular motility: Full OU
- Amsler grid: metamorphopsia OS, unremarkable OD
- Pupils: OD 4 mm → 3 mm light OU; no RAPD
- IOP with applanation: OD 15 mmHg, OS 13mmHg

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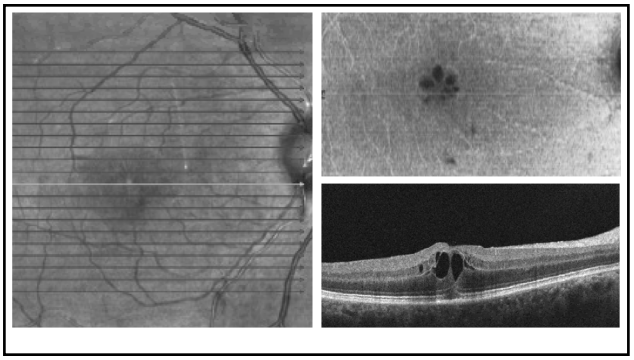

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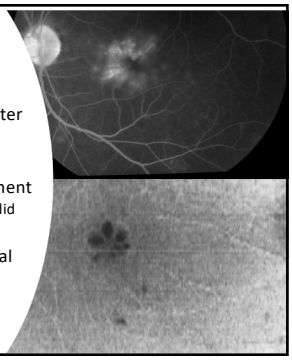
Irvine-Gass Syndrome

- Most common causes of visual loss after uneventful cataract surgery
- Benign, self-limiting, and resolves spontaneously without visual impairment
  - 26.8% of eyes with pseudophakic CME did not recover
- Represents breakdown of blood-retinal barrier due to inflammation
  - VEGF



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Pseudophakic Cystoid Macular Edema

- Prescribe a topical NSAID and a topical steroid in conjunction with the surgeon
- RTCX 3-4 weeks to determine improvement
- Persistent CME
  - steroid injection
  - Anti-VEGF drugs
  - Surgical therapy
    - Pars plana vitrectomy (PPV)

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