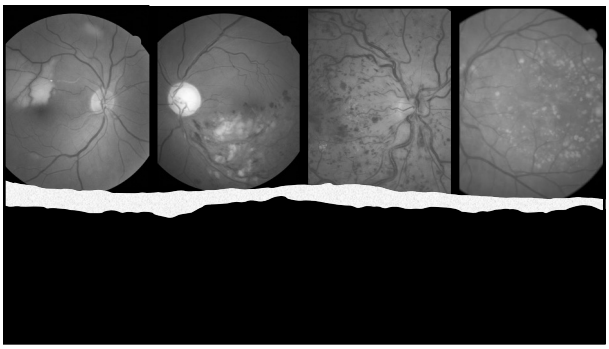


1

Disclosure statement

Sherrol A. Reynolds OD, FAAO, FNAP, FORS

Serve on the speaker bureau, advisory, or contributed board for:

Vision Service Plan (VSP), American Diabetes Association (ADA), Allergan (AbbVie Company), Genentech (Roche), Regeneron

All financial relationships have been mitigated.

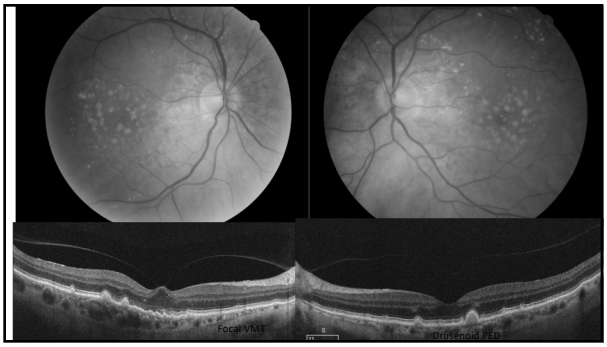
2

Course Agenda

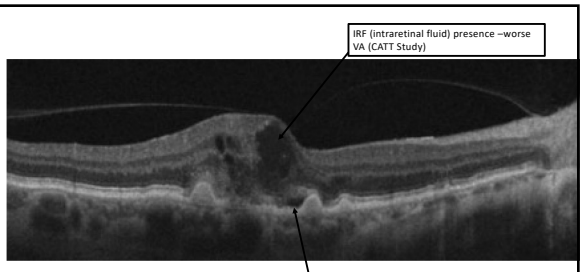
After completion of this course, the participant will be able to:

- Assess new and emerging therapies in retinal disease.
- Explore the role of Photobiomodulation (PBM) and artificial intelligence (AI) in retinal disease.
- Know the latest in gene therapy.
- Be familiar with future trends and challenges in retinal disease.

3

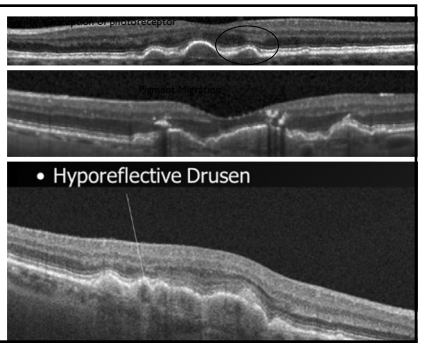


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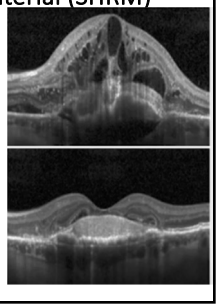
AMD High Risk Biomarkers



6

Subretinal hyperreflective material (SHRM)

- Appears as a bright, reflective layer located between the retinal pigment epithelium (RPE) and the neurosensory retina
  - Neovascular tissue, fibrosis, Fibrin, hemorrhage , proteinaceous exudation
- Presence of SHRM at baseline is strongly indicative of poor BCVA.
- SHRM has been shown to fall with anti-VEGF
- SHRM + IRF presence are highly predictable of vision outcome

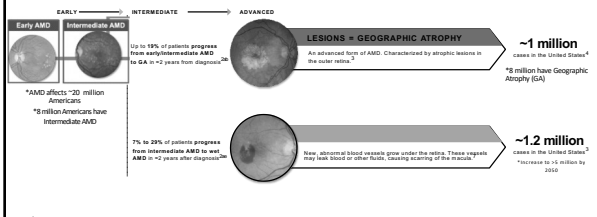


Survey of Ophthalmology
Volume 69, Issue 3, May–June 2024, Pages 362-377

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Age Related Macular Degeneration (AMD):

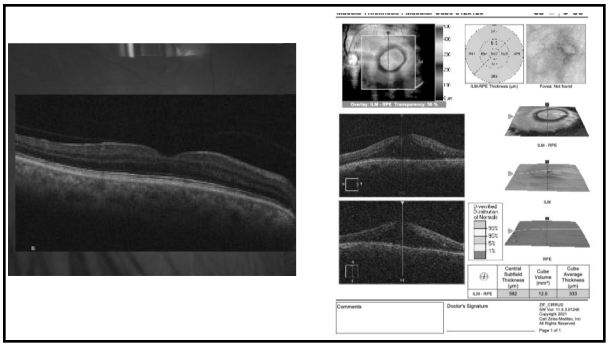
Advance AMD may present as dry geographic atrophy (GA) or wet AMD (neovascular AMD)



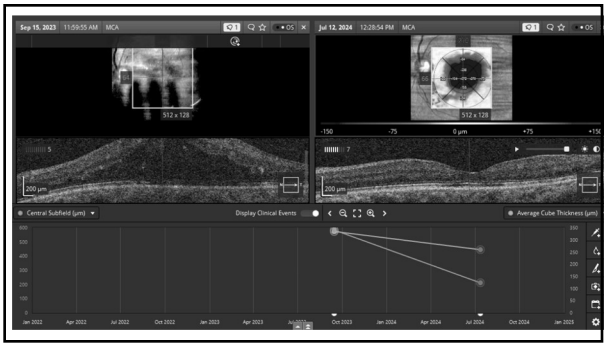
[1]From a retrospective cohort analysis (N=40,543) of a multicenter EMR database from the United Kingdom to estimate rates for progression to GA or wet AMD.
[2]Patients with early or intermediate AMD in one eye and fellow eye with: early or intermediate AMD (4.58%), wet AMD (10.03%), GA (18.6%), both GA and wet AMD (16.58%).
[3]Retrospective cohort analysis (N=913) to assess growth of GA in patients with wet AMD treated with anti-VEGF therapy.
[4]Retrospective analysis of the IRIS database (n=3606/12,339) in patients with GA in the study eye and wet AMD in the fellow eye.
[5]Patients with early or intermediate AMD in one eye and fellow eye with: early or intermediate AMD (7.14%), wet AMD (28.30%), GA (13.87%), both GA and wet AMD (23.31%).

References: 1. Ferris FL 3rd, et al. *Ophthalmology*. 2013;120(4):844-851. **2.** Chakravarthy U, et al. *Ophthalmol Retina*. 2020;4(7):662-672. **3.** Friedman DS, et al. *Arch Ophthalmol*. 2004;122(4):564-572. **4.** Fleckenstein M, et al. *Ophthalmology*. 2018;125(3):369-390. **5.** Xu L, et al. *Retina*. 2015;35(2):176-186. **6.** Rahimy E. Presented at: American Academy of Ophthalmology Meeting; November 14, 2020; virtual. 7. Kassubski F, et al. *Ophthalmol Ther*. 2016;5(4):185-193.

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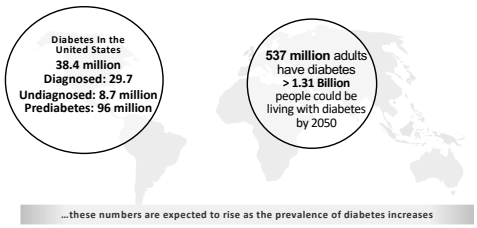


9



10

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



…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

11

Anti-VEGF Patient Treatment Barriers

- Perception of being "too old for therapy"
- Private/professional obligations
- Comorbidities
- Lack of support
- Burden for family members
- Challenge accompanying patients
- Travel/opportunity costs
- Time commitment
- Injection discomfort
- Side effects
- Cost of treatment
- Depression
- Dissatisfaction
- Lack of belief in need for therapy
- Shared decision-making
- Decreased trust in the physician
- Decreased knowledge

Sobolewska B et al. *Clin Ophthalmol*. 2021;15:4317-4326.

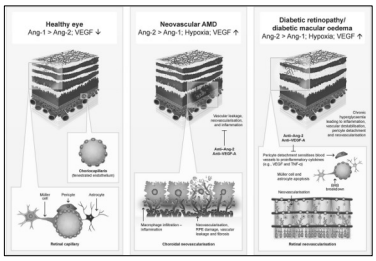
12

New/Emerging Approaches to DME and nAMD Treatment

13

nAMD and DME: What are the Targets?

- Roles of
  - VEGF
  - Ang2
  - Proinflammatory cytokines in DME



Joussen AM et al. *Eye*. 2021;35(5):1305-1316.

14

Anti-VEGF

Ranibizumab 0.5 mg (nAMD)/ 0.3mg (DR/DME) mCNV, RVO
Aflibercept (2.0 mg (0.05 mL)-nAMD, RVO, DME, DR
Brolucizumab 6.0 mg (nAMD, DME)
Faricimab 6.0 mg-nAMD, DME, RVO
Aflibercept HD (8.0 mg)
Biosimilars
Ranibizumab Port Delivery System (PDS)

Bevacizumab/ LYTENAVA (bevacizumab-vikg) Approved 2026

15

Beyond VEGF: Angiopoietin Signaling Pathway

- Angiopoietin pathway involves angiopoietin-1 (Ang-1) and Ang-2, which bind to the Tie2 receptor on endothelial cells, regulating vascular stability and homeostasis.
- Ang-1 primarily promotes vascular stability, while Ang-2 promotes vascular instability.



1. Saharinen P et al. *Nat Rev Drug Discov*. 2017;16(9):635-661. 2. Akwii RG et al. *Cells*. 2019;8(5):471. 3. Heikamp L et al. *Nat Commun*. 2015;6:5962.
Ang-1, angiopoietin-1; Tie2, tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains-2; VEGF-A, vascular endothelial growth factor-A; VEGFR2, vascular endothelial growth factor receptor-2

16

EXTENDED TREATMENT FOR AMD, DME, RVO (ME)

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

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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RHONE-X Demonstrated Long-Term Safety and Efficacy of Dual Ang-2/VEGF-A Inhibition With Faricimab in DME

RHONE-X s the largest DME extension study to date and had high patient retention (81.7%)

- **BCVA and CST improvements** in YOSEMITE/RHINE were **maintained** with ~80% of patients on ≥ Q12W dosing at the end of study
- **Absence of DME** (CST < 325 µm) was achieved in **more than 90% of patients** by the end of the study
- First **absence of DME** was **achieved faster** by patients starting on **faricimab** vs aflibercept
- Faricimab was **well tolerated** with a safety profile that was **consistent** with YOSEMITE/RHINE

Lai TYY. Presented at Retina Society Annual Scientific Meeting; Lisbon, Portugal; September 11-15, 2024.
Ang-2, angiopoietin-2.

QUASAR Phase 3 trial

- Confirms extended dosing efficacy for RVO macular edema

Pulsar and Photon Extension studies:

At 3 years of aflibercept 8 mg treatment for nAMD and DME the vast majority of patients maintained visual and anatomic improvements.

- PULSAR (wAMD): 58% of patients had a last assigned interval of at least 4 months, with 24% reaching 6 months.
- PHOTON (DME): 88% of patients had a last assigned interval of at least 12 weeks, and 48% had at least 20 weeks.

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Ranibizumab Port Delivery System with (Susvimo)

Continuous intravitreal delivery of a customized formulation of ranibizumab

Innovative drug delivery system FDA approved 10/2021 for treatment of nAMD

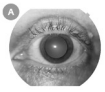
Refillable ocular implant

Customized formulation of ranibizumab 100 mg/mL

Implant surgically placed at the pars plana

In-clinic refill-exchange procedures

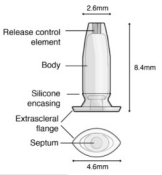
Voluntary recall 10/2022: "pause in all new implantations"
- Issues during repeat puncture
- Updated implant and needle
- Reintroduced 6/2024

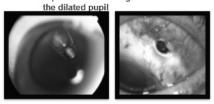


In panel A, the eye is in the **primary position** and the implant is **not visible**



In panel B, the eye is **looking up** and temporally, and the implant is **seen through the dilated pupil**





Holekamp, Nancy M., et al. "Archway Randomized Phase 3 Trial of the Port Delivery System With Ranibizumab for Neovascular Age-Related Macular Degeneration." *Ophthalmology* (2021).

19

Ranibizumab PDS for nAMD: Archway and Portal Trials

- **Archway – phase 3 trial PDS 100 mg/mL nAMD**
  - 418 patients with recently diagnosed nAMD who had previously responded to anti-VEGF therapy
  - PDS Q24W demonstrated noninferior and equivalent efficacy to monthly ranibizumab, with 98.4% of PDS-treated patients not receiving supplemental treatment in the first 24-week interval
  - Q24W refill dosing
- **Portal – long-term extension study of ladder and Archway studies**
  - Q24W refill dosing
  - Approximately half of all participants had vision equivalent to 20/40 or better at year 5

Interim Results of the Phase III Portal Extension Trial of the Port Delivery System with Ranibizumab in Neovascular Age-Related Macular Degeneration. Ophthalmology Retina , 2024, 9, 144-155

20

Ranibizumab PDS for DME/DR

DME Pagoda
- Phase 3 trial: Evaluate safety and efficacy of PDS 100 mg/mL Q24W for DME
- A 64-week, randomized study of SUSVIMO vs monthly ranibizumab injections for DME.
- Study found that BCVA from baseline averaged noninferior for PDS every 24 weeks vs monthly ranibizumab.

DR Pavilion
- PDS 100 mg/mL Q36W for NPDR without CI-DME compared to monitoring.
- At 1 year, PDS Q36W resulted in substantially more participants achieving at least a 2-step DRSS improvement and a reduced risk of developing CI-DME or PDR compared with control participants, with safety outcomes consistent with previous reports.

Investigative Ophthalmology & Visual Science June 2024, Vol.65, 6232

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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."

Ranibizumab Biosimilars
- Byooviz (Samsung)
- Cimerli (Coherus)

Aflibercept Biosimilars
- Yesafili
- Opuviz
- Ahzantive
- Enzeevu
- Pavblu

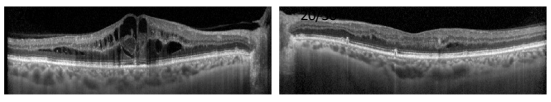


Concerns about biosimilar safety, efficacy, and immunogenicity

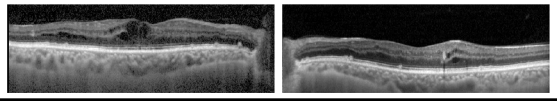
22

OD
- q4-5w aflibercept x 20
- q4-5w faricimab x 3
- Switch to dexamethasone 0.7 mg implant

OS
- q4-5w aflibercept x 6
- q4-5w faricimab x 3
- Continue faricimab



6 weeks



23

PALADIN and REINFORCE Trial for DME

Fluocinolone (Fac) for DME
- The 0.19-mg fluocinolone acetonide (FAc) implant was approved by the FDA in 2014 for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP.
- **Patients experienced a 70.5% reduction in overall median treatment frequency, dropping from 3.4 treatments per year down to just 1 treatment per year.**
- Mean intraocular pressure (IOP) remained stable throughout the trial. An IOP rise above 30 mmHg occurred in 10.89% of eyes, and the rate of IOP-related surgery was 2.97%

Dexamethasone Intravitreal Implant (DEX) in DME
- Phase 4, prospective, multicenter observational trial evaluating the real-world use of the 0.7 mg dexamethasone intravitreal implant (DEX)—known as Ozurdex
- **Mean maximum best-corrected visual acuity improved by +9.1, +7.7, and +7.0 letters after the first three injections. Overall, 36.0% of eyes achieved a gain of 15 letters or more**

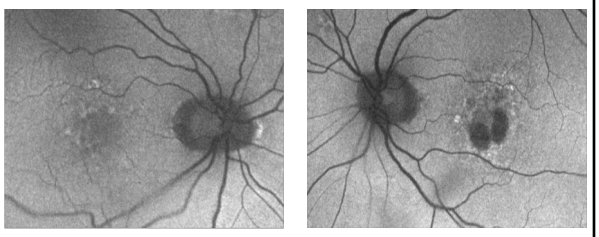
Singer MA et al. *Ophthalmology*. 2022;129(6):605-613.
Singer MA. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49(8):425-435.

24

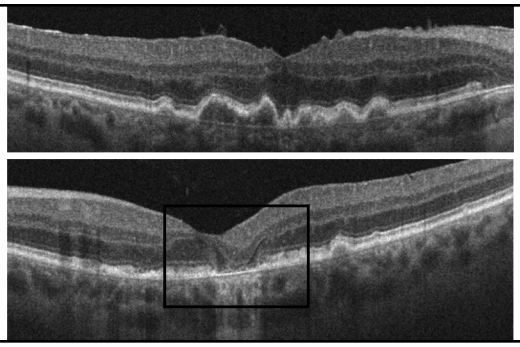
2026: Phase 3 DIAMOND trial of topical OCS-01 (high-concentration dexamethasone drops

- Evaluated OCS-01 (a topical 1.5% dexamethasone ophthalmic suspension)
  - Randomized, multi-center Phase 3 trials (DIAMOND-1 and DIAMOND-2)
  - Over 800 patients enrolled across 119 investigative sites.
  - Regimen: Patients received OCS-01 or vehicle eye drops 6 times daily for a 6-week induction phase, followed by 3 times daily through week 52.
  - Primary Endpoint: Mean change in Best Corrected Visual Acuity (BCVA ETDRS letter score) at week 52.
- **June 2026**
  - **Primary Endpoint Missed: Neither DIAMOND-1 nor DIAMOND-2 met the 52-week primary visual acuity endpoint, and secondary ≥15-letter BCVA gain endpoints were also missed**

25



26

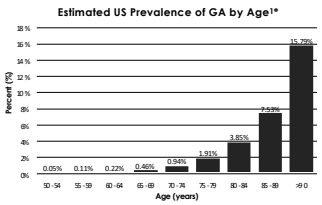


27

The Prevalence of GA Will Continue to Increase

4x From age 50, the prevalence of **GA quadruples every 10 years**

2x The proportion of the **population >60 years of age will nearly double** from 2015 to 2050[3]



*Age-group specific prevalence estimates applied to the 2011 United States white population in 5-year age bands.

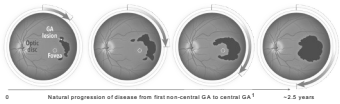
1. Rudnicka AR, et al. *Ophthalmology*. 2012;119(3):571-580. 2. Wong WL, et al. *Lancet Glob Health*. 2014;2(2):e106-e116. 3. World Health Organization. Ageing and health. Updated October 1, 2022. Accessed October 22, 2022. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

28

Lesions associated with GA cause progressive visual impairment as the areas of atrophy expand toward the fovea

In a long-term AREDS study (N=3640), lesions encroached the fovea in a median of just **2.5 years** in a retrospective subpopulation analysis of 397 patients[2a]

- As lesions progress and expand into the fovea, **central vision is severely impaired**[2]
- However, even before reaching the center of the fovea, **lesion growth may cause visual impairment**[2]
- **Lesion growth can affect aspects of functional vision like reading and driving, even if BCVA is relatively unchanged**[4]





Early intervention could slow lesion progression[3]

AREDS=Age-Related Eye Disease Study; BCVA=best-corrected visual acuity; GA=geographic atrophy.
[a]Data from AREDS 400, a long-term, multicenter, prospective study examining progression of GA area in a cohort of 3640 patients with signs of early and more advanced forms of AMD.

References: 1. Boyer DS, et al. *Retina*. 2017;37(5):819-835. **2.** Lindblad AS, et al. *Arch Ophthalmol*. 2009;127(9):1168-1174. **3.** Fleckenstein M, et al. *Ophthalmology*. 2018;125(3):369-390. **4.** Kimel M, et al. *Invest Ophthalmol Vis Sci*. 2016;57(14):6288–6304.

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Multimodal Imaging of GA lesions

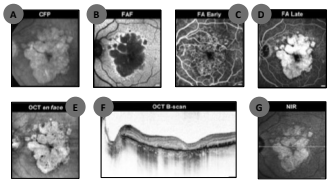
A: Color fundus photography

B: Fundus autofluorescence

C-D: Fluorescein angiography (over course of exam)

E-F: Optical coherence tomography

G: Near-infrared reflectance

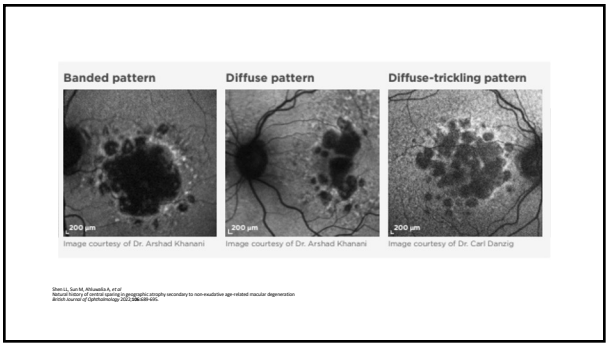


Fleckenstein M, et al. 2018.

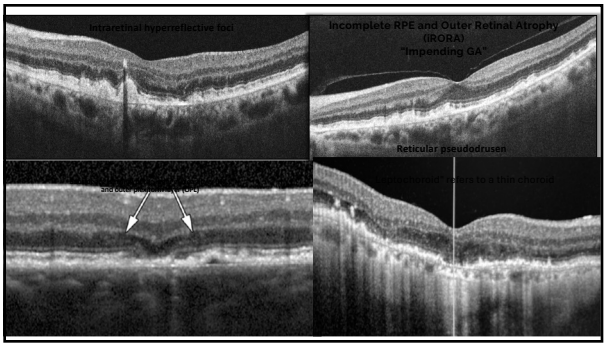
GA=geographic atrophy.

Reference: 1. Fleckenstein, et al. *Ophthalmology*. 2018;125(3):369-390.

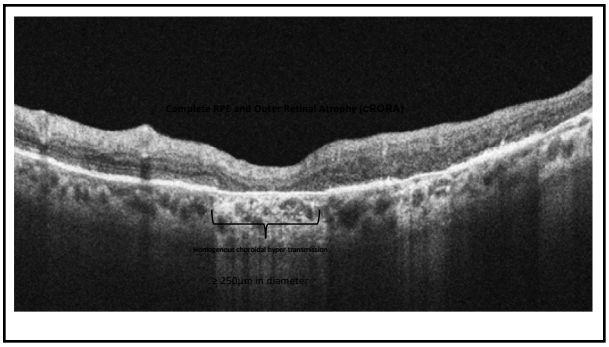
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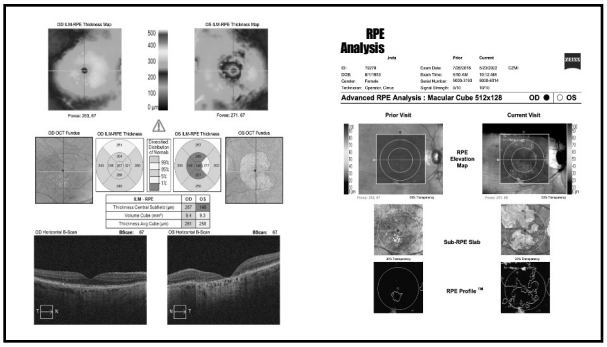
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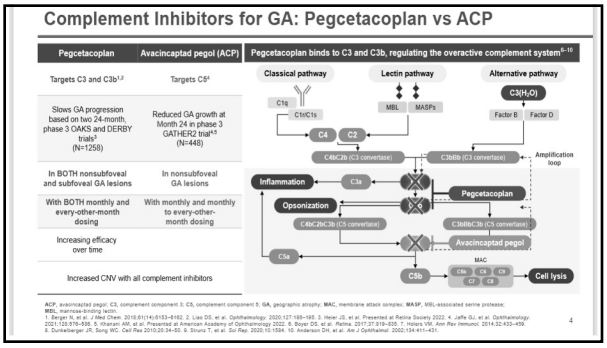
34

Geographic Atrophy (GA) Treatment

Syfovre (pegcetocoplan)	Izervay (avancincaptad pegol)

• **Apellis**
• FDA approved Feb 17, 2023
  • One injection every 25 to 60 days
• Slows progression of GA by blocking C3
  • OAKS Study: 22% qm, 18% qom
  • DERBY: 18% qm, 17% qom
  • Increasing effect with time
• Recent concern of vasculitis
	• **Astellas**
	• FDA approved Aug 5, 2023
	  • One injection per mos for up to 12 mos
	• 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

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Adverse Events: Rates of Progression to CNV/Exudation

Pegcetacoplan

	EXUDATIVE AMD*
PM (n=419)	12%
PEOM (n=420)	7%
Sham (n=417)	3%

*Investigator-reported CNV or neovascular AMD
- Pts who developed neovascular AMD continued PEG with anti-VEGF in addition per investigator discretion
- No pts discontinued study due to neovascular AMD

Avacincaptad Pegol

MNV and Exudative MNV in the Study Eye at Month 12

GATHER① GATHER②

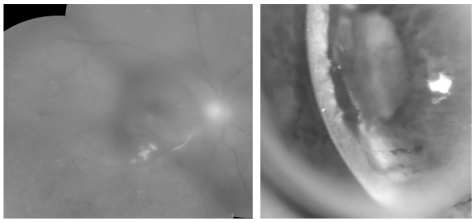
	ACP 2 mg (N=470)*	Sham (N=1 [0])*	ACP 2 mg (N=223)	Sham (N=222)
Total MNV, n (%)	4 (1.0)	3 (2.7)	15 (4.7)	9 (4.1)
eMNV, n (%)	4 (6.0)	3 (2.7)	11 (4.9)	7 (3.2)
neMNV, n (%)	2 (3.0)	0	1 (0.4)	0
Peripapillary NV, n (%)	0	0	3 (1.3)	2 (0.9)

Risk of CNV exists with both meds

Jaffe GJ, et al. *Ophthalmology*. 2021;128(4):576-586.
Chiang A, et al. Presented at: ARVO 2023; April 23-27, 2023; New Orle

37

Adverse Events: Intraocular Inflammation (IOI)



38

All cases after the first injection.

Presentation: 8-23 days



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[1], Glenn J. Jaffe, MD[2], Sunil K. Srivastava, MD[3], Janet L. Davis, MD[4], and Judy E. Kim, MD, FARVO, FASRS[5] and the ReST Committee

VA at baseline: 20/30-5/200

VA at last FU 20/70-NLP

100%with AC inflammation 86% with vitritis.

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

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Longterm Outcomes

GALE is the extension study for OAKS and DERBY and provided a look at 36 months of continuous treatment with pegcetacoplan

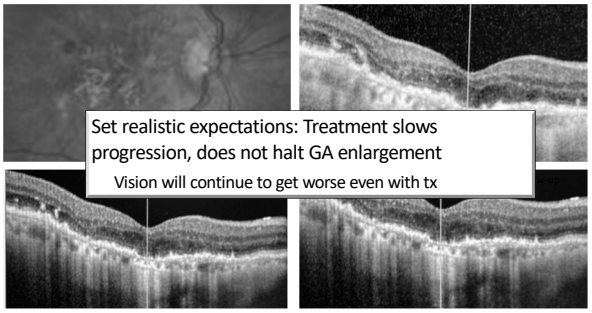
- **Reduced GA lesion growth with both monthly (35%; P<0.0001) and every-other-month (EOM) (24%; P<0.0001) treatment compared to the projected sham arm.**
- Reduced non-subfoveal GA lesion growth with both monthly (42%; P<0.0001) and EOM (28%; P=0.0015) treatment compared to the projected sham arm.
- Reduced GA lesion growth by 19% (P<0.0001) after one year of Syfovre treatment (combined monthly and EOM), compared to the sham treatment period, in patients who crossed over from the sham group.

Open-label extension (OLE) trial of the phase 3 GATHER2

- 40.5% versus projected sham in patients who switched from Izervay monthly (EM) or every-other-month (EOM) to Izervay EM at 3.5 years
- 37% versus projected sham in patients who previously received sham and then switched to Izervay EM (P<0.001 for both comparisons).

American Journal of Ophthalmology Volume 276, August 2025, Pages 350-364

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Set realistic expectations: Treatment slows progression, does not halt GA enlargement

Vision will continue to get worse even with tx

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Extending The Complement Inhibitors for GA

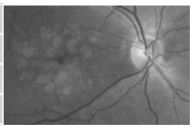
- ANX007 intravitreal injection for geographic atrophy
  - Non-pegylated antigen-binding fragment (Fab) designed to block C1q locally in the eye with an intravitreal formulation
    - C1q is thought to be a key driver of neurodegeneration
- Phase 2 Analyses from ARCHER
  - 61 patients were randomized to receive either a 5 mg dose of ANX007 every month, every other month, or sham treatment.
  - After one year of treatment, the risk of losing three lines of vision or more as measured by an eye chart was reduced by 72 percent in patients treated monthly (P = .006), and by 48 percent in patients treated every other mon

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Intermediate AMD Risk

5-YEAR RISK OF PROGRESSION TO ADVANCED AMD

Early AMD	1.3% (either eye)
Intermediate AMD	18.3% (either eye)
Fellow eye intermediate AMD	27.0%
Fellow eye advanced AMD	42.9%



- Monitor more frequently (~3 to 6 months)
- Home self-screening (amsler/Foresee home)
- OTC AREDS 2 supplements
- Consider Photobiomodulation

Age-Related Eye Disease Study Research Group. Arch Ophthalmol. 2001;119:1417-1436.
Bäarnäe M, et al. Optom Vis Sci. 2011;88(7):881-889.
Seddon JM, et al. JAMA Ophthalmol. 2013;131(4):448-455.

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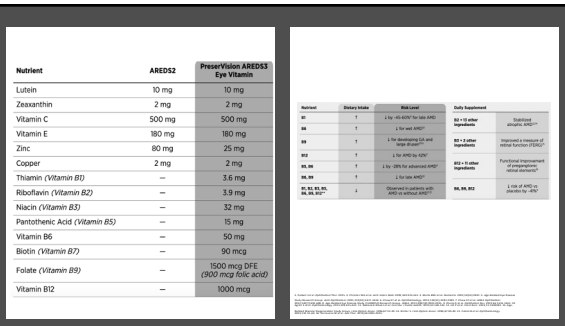
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Where did the B-vitamin idea come from?

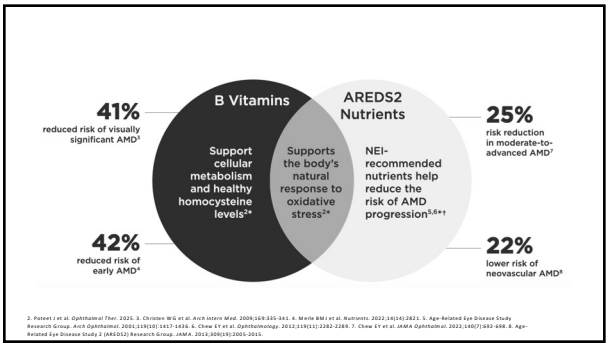
- Researchers gave about 5,200 women with heart disease, or a high risk of it, three B vitamins, folic acid, B6, and B12, or a placebo, and followed them for about seven years.
- By circumstance, the women taking the B vitamins developed fewer cases of macular degeneration, 55 compared with 82, roughly a third fewer.
- The addition of B vitamins is based on retrospective data and narrative reviews (such as the WAFACS study) linking B vitamins to lower homocysteine and reduced AMD risk, but prospective clinical trials directly testing the combined AREDS3 formula are still in planning
- It tested three B vitamins, and AREDS 3 contains eight.
- Nobody has run the AREDS 3 combination against AREDS 2 head to head.

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Nutrient	AREDS2	PreserVision AREDS3 Eye Vitamin
Lutein	10 mg	10 mg
Zeaxanthin	2 mg	2 mg
Vitamin C	500 mg	500 mg
Vitamin E	180 mg	180 mg
Zinc	80 mg	25 mg
Copper	2 mg	2 mg
Thiamin *(Vitamin B1)*	—	3.6 mg
Riboflavin *(Vitamin B2)*	—	3.9 mg
Niacin *(Vitamin B3)*	—	32 mg
Pantothenic Acid *(Vitamin B5)*	—	15 mg
Vitamin B6	—	50 mg
Biotin *(Vitamin B7)*	—	90 mcg
Folate *(Vitamin B9)*	—	1500 mcg DFE *(900 mcg folic acid)*
Vitamin B12	—	1000 mcg



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Photobiomodulation therapy (PBMT) Updates

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Photobiomodulation (PBM)

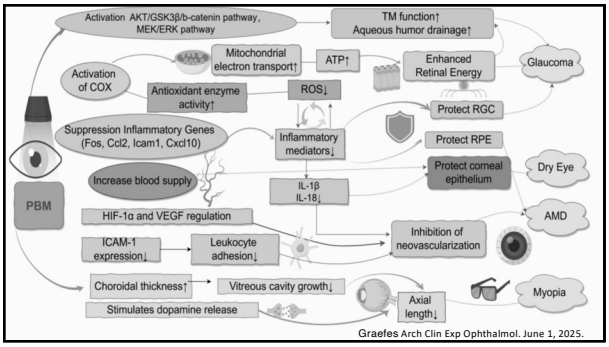
- Non-invasive therapy that delivers specific wavelengths of visible to near-infrared light (roughly 500–1000 nm.
- Primary mechanism is the photoactivation of cytochrome c oxidase (Complex IV), a key enzyme in the mitochondrial electron transport chain.
- Enhances the electron transport chain, increases ATP production, and improves cellular bioenergetics in metabolically demanding retinal cells

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Photobiomodulation Works at the Cellular Level

- **Macrophage polarization:** PBM promotes the shift from the pro-inflammatory M1 phenotype to the reparative M2 phenotype, which is central to wound healing and inflammation control.
- **Angiogenesis:** PBM upregulates VEGF and HIF-1α while suppressing pro-inflammatory cytokines TNF-α, IL-1β, and IL-6.

50



Graefes Arch Clin Exp Ophthalmol. June 1, 2025.

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Photobiomodulation for Dry AMD

- FDA-authorized therapy for Dry AMD using Photobiomodulation
- LIGHTSITE III
  - 100 subjects, 148 eyes; 24-month analysis; randomized PBM to sham 2:1
    - Active sham
  - High-risk intermediate AMD
  - Improves cellular processes (cytochrome c oxidase in the mitochondria at the level of the electron transport chain)
- **Primary endpoint met!**
  - Difference between treatment and sham group at 13 months (and 2 years!)
    - 5.5 letters at month 13, 5.9 at month 24
    - PBM group: decrease in new-onset GA

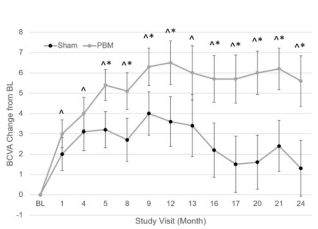
FDA approved for Dry AMD to improve Vision (November 4th, 2024)
Photobiomodulation
Data from two-year LIGHTSITE III trial

52

Photobiomodulation (PBM) - Valeda Light Delivery System

LIGHTSITE III 24-month study

- Met the predetermined primary efficacy BCVA endpoint at Month 21 (mean letter difference of 3.8 letters, p = 0.0036) with a statistically significant difference between the PBM group versus Sham
- A mean letter difference of 4.3 letters (p = 0.0024) was maintained at Month 24.
- Within group analysis showed improved BCVA with a mean > 5 letter gain in PBM eyes from:
  - Month 13 (LS mean 6.0 letters) (p = < 0.0001)
  - Month 21 (LS mean 6.2 letters) (p < 0.0001)
  - Month 24 (LS mean 5.6 letters) (p < 0.0001)



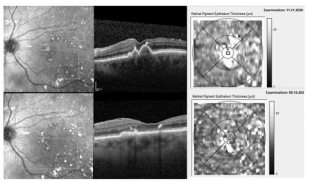
*LS mean presented with multiple imputation. *, p < 0.05 between groups; ^, p<0.05 within groups.*

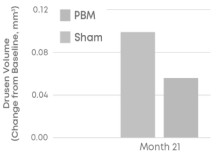
53

Photobiomodulation (PBM) - Valeda Light Delivery System

LIGHTSITE III 24-month study

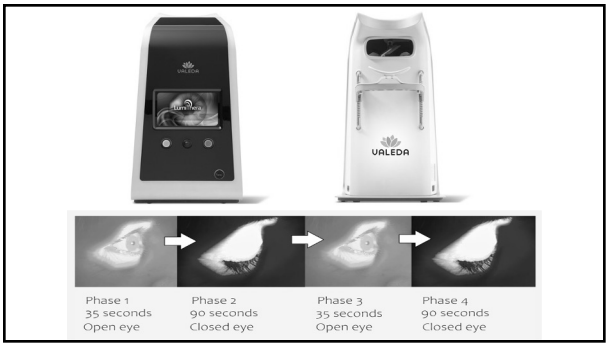
- A greater numerical increase in macular drusen volume observed in sham vs PBM grp





Example pt treated with PMB with drusen volume reduction at month 13

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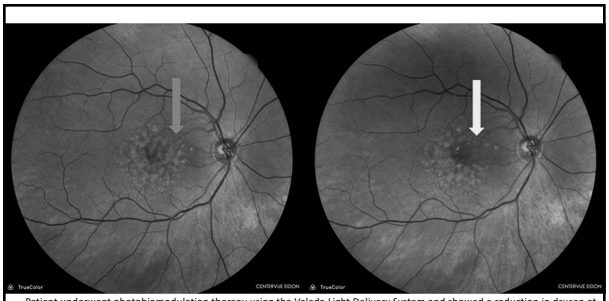
55

Photobiomodulation

- Less than 5 minutes per session, no dilation
- 9 sessions over 3-5 weeks; every 4 months over 24 months (LIGHTSITE III)
  - 590 nm (yellow), 66 nm (red), and 850 nm (NIR)



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Patient underwent photobiomodulation therapy using the Valeda Light Delivery System and showed a reduction in drusen at the 1-year follow-up examination.

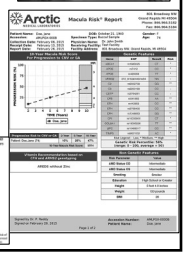
Siqueira RC. Photobiomodulation Using Light-Emitting Diode (LED) for Treatment of Retinal Diseases. *Clin Ophthalmol*. 2024:18:215-225.

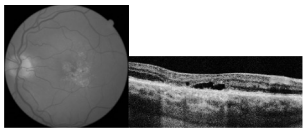
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Precision Medicine Example: AMD Macula Risk Test *(Arctic Medical Laboratories)*

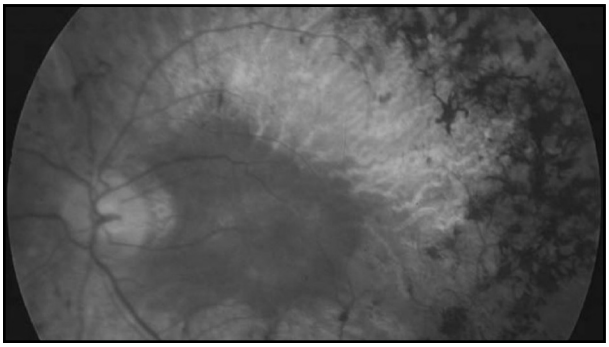
- Gives risk of progression to wet AMD
- Suggests supplements based on presence/absence of specific alleles of CFH, ARMS2, and other genes
  - AREDS with or without zinc
  - Zinc alone
  - Antioxidants alone







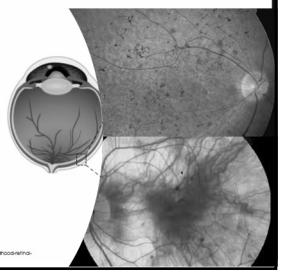
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Monogenic Disease in the Eye: Inherited Retinal Diseases (IRDs)

- 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. Daiger et al. Cold Spring Harb Perspect Med. 2014;4(12):a017111. 2. AAO. https://www.aao.org/eyenet/article/childhood-retina-

60

Gene Therapy for Inherited Retinal Diseases (IRD)

- Genetic modification of DNA to produce a therapeutic effect by replacing a mutated gene, adding a missing gene or modifying an existing one.
- Genes may be introduced into cells through a vector, usually a virus
  - Adeno-associated viruses (AAV) are used in gene therapy due to their unique biology, simple structure and poorly immunogenic response compared with other viruses
- **Voretigene neparvovec-rzyl (Luxturna™)**



single dose for each eye, of 1.5 x 10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL

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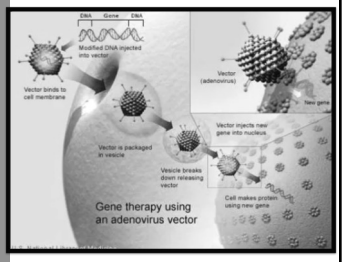
Retina Gene Therapy Updates

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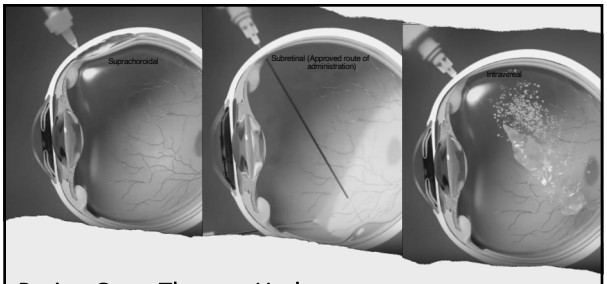
BASICS OF GENE THERAPY

Delivery of DNA into cells

- Viral Vector
  - Recombinant viruses- viral vector
  - Naked DNA or DNA complexes- NON-Viral Vector
  - Adeno-associated viral vector (AAVs)
    - AAV8 serotype



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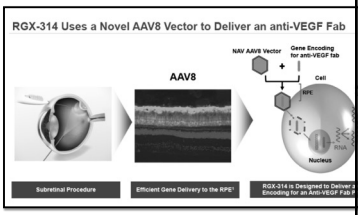
Retina Gene Therapy Updates

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AMD Gene Therapy-RGX-314 (Surabgene Lomparvove)

AbbVie and REGENXBIO

- Phase 3 clinical trial- one-time treatment for wet age-related macular degeneration (wet AMD) and diabetic retinopathy
- Adeno-associated virus (NAV AAV8) vector-based gene
- It encodes an antibody fragment designed to inhibit vascular endothelial growth factor (VEGF)
- Suprachoroidal delivery
- ATMOSPHERE and ASCENT Clinical Trials – wet AMD
- ALTITUDE (Phase II) for DR



REGENXBIO announces completion of enrollment in pivotal trials of subretinal suraabgene lomparvovec for Wet AMD. Published October 6, 2025. Accessed October 9, 2026. https://ir.regenxbio.com/news-releases/news-release-details/regenxbio-announces-completion-enrollment-pivotal-trials

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REGENXBIO®

REGENXBIO Presents Positive Long-Term Data for Surabgene Lomparvovec in Wet AMD and Diabetic Retinopathy at American Society of Retina Specialists Annual Meeting

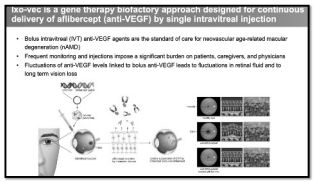
July 18, 2026 02:55 PM EDT

- *One-time gene therapy treatment with sura-vec demonstrated long-term efficacy at similar doses to those being evaluated in ongoing late-stage studies:*
  - *Stable to improved vision through 5 years in wet AMD patients who required frequent anti-VEGF injections prior to one-time sura-vec; no drug-related IOI observed in a setting of no prophylactic steroids*
  - *Prevention of vision-threatening events without any additional treatment and ≥2-step DRSS improvement in majority of NPDR participants at 2.5 years; no IOI observed with short-course prophylactic topical steroids*
- *Topline data from wet AMD pivotal studies, ATMOSPHERE® and ASCENT®, expected in Q4 2026*

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Ixoberogene soroparvovec (Ixo-vec; ADVM-022)

- Ixo-vec (AAV.7m8-aflibercept) delivers a continuous aflibercept-producing gene via a single in-office intravitreal (IVT) injection
- Earlier: Luna/Optic
- Phase 3 ARTEMIS Trial
  - IVT injection of Ixo-vec (at 6E10 vg/eye) versus active-comparator aflibercept 2 mg every 8 weeks



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OCU410—Gene Therapy for the Treatment of Geographic Atrophy (GA)

- OCU410 utilizes an adeno-associated virus (AAV) platform for the retinal delivery of the *RORA* (ROR Related Orphan Receptor A) gene
- RORA protein plays an important role in lipid metabolism, reducing lipofuscin deposits and oxidative stress, and demonstrates an anti-inflammatory role as well as inhibiting the complement system.
- Phase II

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JNJ-1887

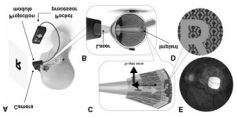
- Phase 1, open label; 17 patients with GA secondary to dry age-related macular degeneration
  - Low, intermediate, high dose; without steroid prophylaxis
    - Observed over 24 months
- Targets CD59; downstream target that inhibits MAC formation
- Single intravitreal injection; sustained production of secreted CD59 that diffuses into the outer retina
- 29% mild ocular inflammation, resolved with topical steroids or observation
  - No CNV through 24 months

Heier JS, Cohen MN, Chao DL, Pepin A, Shiraga Y, Capuano G, Rogers A, Ackert J, Sen HN, Csaky K. Phase 1 Study of JNJ-81201887 Gene Therapy in Geographic Atrophy Secondary to Age-Related Macular Degeneration. Ophthalmology. 2024 Dec;131(12):1377-1388.

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Vision restoration after photoreceptor loss

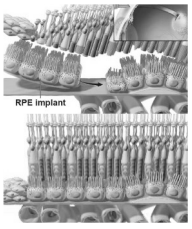
- **Optogenetics** (gene-agnostic light-sensitive proteins introduced into surviving inner retinal cells) has produced published partial functional recovery in ganglion-cell–targeted and bipolar-cell–targeted patients; MCO-010 is in trials.
- A **subretinal photovoltaic implant combined with external goggles** restored some visual function in geographic atrophy, and stem/iPSC-based cell replacement continues in early trials
  - PRIMA system



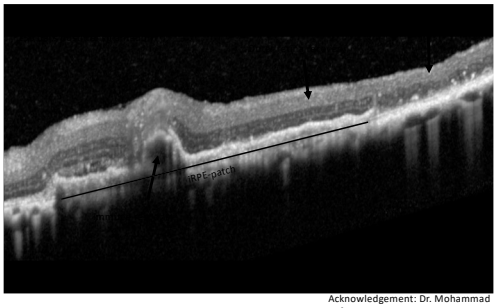
70

Stem Cell and Transplantation for AMD/GA

- Dry AMD
  - Stem cell-derived RPE patches and secretome injections are in development.
  - In Phase 2b trials, the RPE patch improved vision in 27% of patients over three years.
- Wet AMD
  - Stem cell-derived retinal pigment epithelium patches have been implanted in patients with wet AMD.
  - These patches have shown safety and effectiveness.
- Clinical trials: Multiple clinical trials are underway for stem cell therapies for dry and wet AMD.



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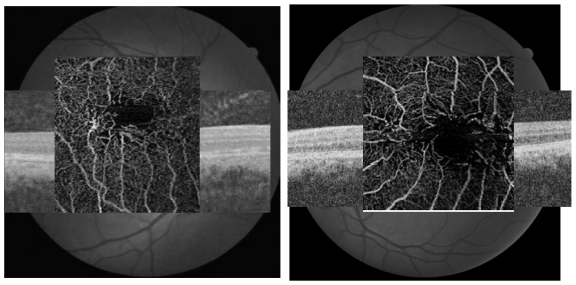


Acknowledgement: Dr. Mohammad Rafieetary

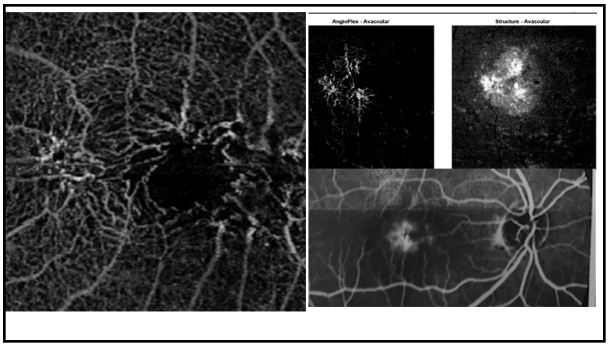
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Retina Neuroprotection
Ciliary neurotrophic factor (CNTF)
Updates

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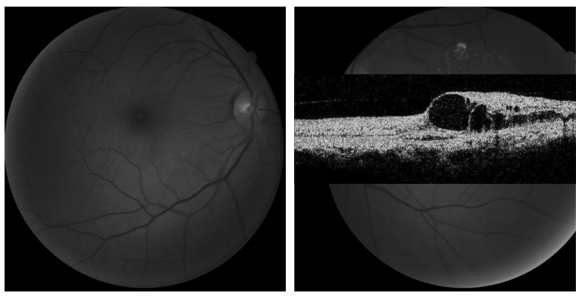


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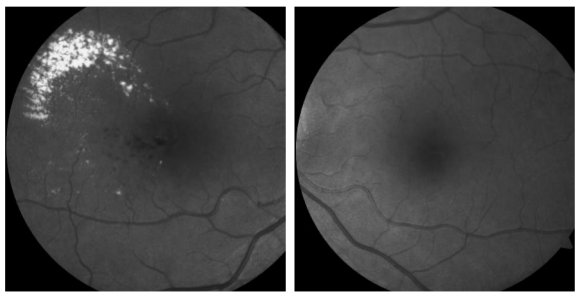
Macular Telangiectasia (MacTel)

- Poorly Understood Degenerative Retinal Disorder
- Retinal neurovascular and glial degenerative disease
  - 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

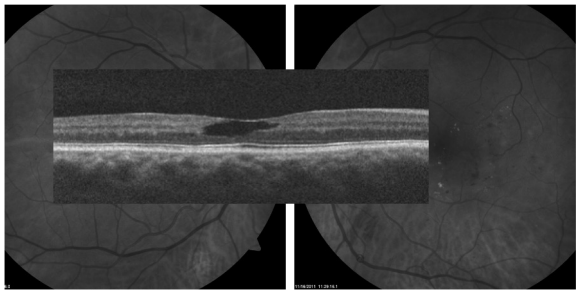
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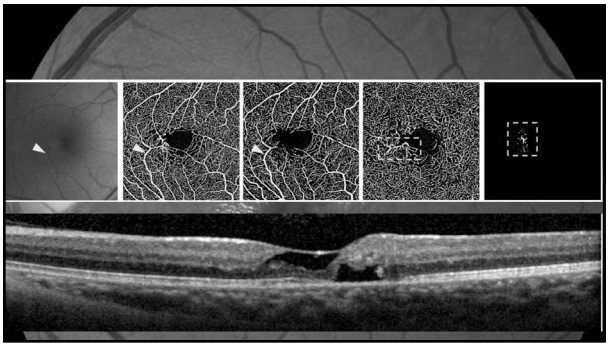


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Macular Telangiectasia (MacTel)

- 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 and nAMD

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Macular Telangiectasia (MacTel)

- 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
- MacTel 2 50% Type 2 will have better than 20/30 rarely 20/200

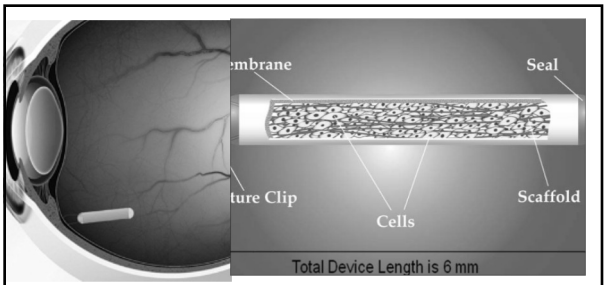
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Ciliary neurotrophic factor (CNTF)

- ENCELTO (revakinagene taroretcel-lwey) FDA approved March 2025 to treat macular telangiectasia type 2 (MacTel 2)
- 1st FDA approved treatment to slow progression of MacTel 2
- Allogeneic encapsulated cell-based gene therapy (ECT), surgically implanted into the vitreous and sutured to the sclera in an outpatient procedure
- Sustained release of CNTF for up to 14 years, slow photoreceptor degeneration
- Phase III results? Rate of change in ellipsoid zone (EZ) area loss from baseline through 24 months 56.4% rate of reduction in Protocol A ($p<0.0001$) and 29.2 % rate of reduction in Protocol B ($p=0.021$)
- Ideal candidates?

Neurotech's ENCELTO (revakinagene taroretcel-lwey) approved by the FDA for the treatment of macular telangiectasia type 2 (MacTel). Press release. Neurotech Pharmaceuticals. Published October 4, 2025. Accessed March 6, 2025. https://www.neurotechpharmaceuticals.com/neurotechs-revolutionary-treatment-neurotrol-lwey-approved-by-the-fda-for-the-treatment-of-macular-telangiectasia-type-2-mactel/

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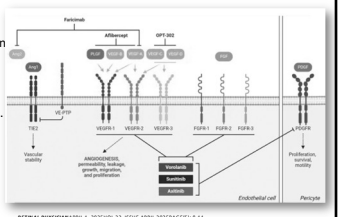
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New MOA under investigation in nAMD/ DR

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New MOA under investigation in nAMD/ DR

- **Tyrosine Kinase Inhibitors(TKIs) for AMD/ DR**
- TKIs are small molecules that work by inhibiting enzymes from phosphorylating tyrosine residues, thereby blocking downstream activation of VEGF, platelet-derived growth factor (PDGF), fibroblast growth factor, and more than 50 other receptor tyrosine kinases.
- TKIs for the VEGF and PDGF receptors
- TKIs being investigated :
  - Vorolanib
  - Sunitinib
  - Axitinib

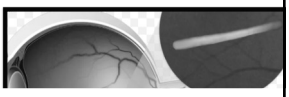


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DURAVYU 2.7 mg (Eye Point Pharmaceuticals)

- Sustained-delivery, intravitreal (IVT) insert that delivers the tyrosine kinase inhibitor (TKI) vorolanib
  - Vorolanib is a potent and highly selective TKI that acts intracellularly by binding to all 3 VEGF receptors
  - Durasert E technology to provide a



News | **Articles** | October 20, 2026

Modern Retina Ophthalmology

- **Duravyu misses wet AMD end point again as EyePoint pivots to DME**

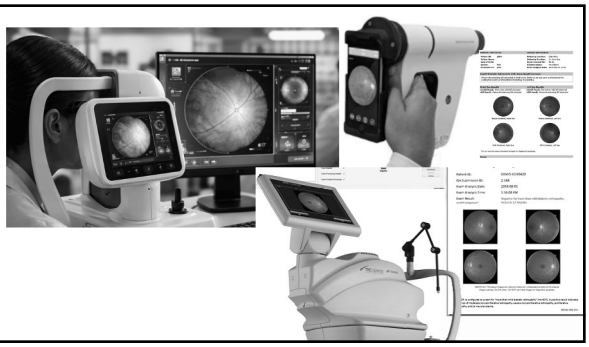
Author(s) Kassi Filkins

- *Second phase 3 trial of Duravyu misses wet AMD noninferiority end point; EyePoint cuts 53% of staff to focus on DME.*

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Artificial Intelligence (AI) Imaging advances for Retina

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AI for Diabetes Screening

- The Topcon IDx-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
- The Remidio FOP device was found to have high sensitivity and specificity for the detection of any grade of DR with good agreement between graders. The rate of ungradable images was acceptably low and image quality was marginally better with the Remidio FOP

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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.[29] 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.

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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Artificial Intelligence (AI) in Monitoring AMD

- FDA Authorized , AI-Powered
- Approved in 2024
- OCT images in a 10x10-degree area centered on the point of fixation
- AI-based program that segments and estimates the volume of hyporeflective spaces on OCT image.

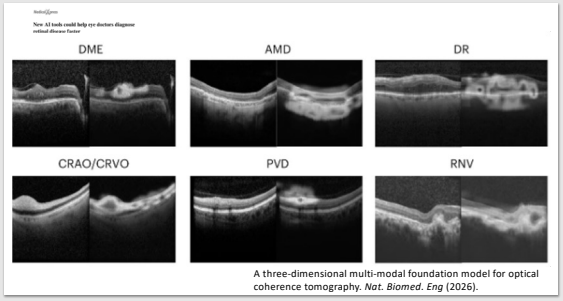


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Major AI Breakthroughs and Applications in 2026

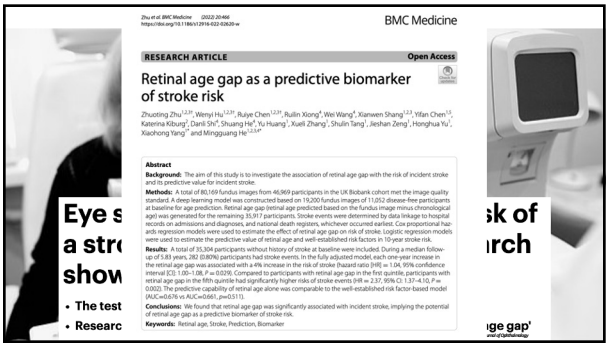
- **3D Scan Analysis (OCTCube-M):** WashU Medicine and partners developed experimental AI systems like **OCTCube-M** to interpret hundreds of 2D slices inside 3D optical coherence tomography (OCT) scans, cutting down manual review time and tracking diseases like age-related macular degeneration (AMD).
- **Multidisease Screening (Reti-Pioneer):** Published in *Nature Medicine*, the **Reti-Pioneer** AI framework analyzes eye scans to spot signs of diabetes, osteoporosis, high blood pressure, high cholesterol, gout, and thyroid disease in seconds.
- **Retinal Biological Age:** A study from Tohoku University and models published in *Communications Medicine* use AI on single fundus photos to estimate a person's "retinal age," flagging hidden risks for major systemic conditions
- Autonomous Diabetic Retinopathy Tool

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A three-dimensional multi-modal foundation model for optical coherence tomography. *Nat. Biomed. Eng* (2026).

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Future Trends and Challenges

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Future Trends and Challenges

- Artificial Intelligence (AI)- We are likely to see more FDA approved AI systems
  - iCare ILLUME (Centervue) and iPrevent DR (iHealthScreen)
- Advancements in Imaging modalities
  - OCTs
  - Widefield OCTA and panoramic full range capabilities
- Gene therapy/ stem cell
- New MOAs
  - Sozinibercept (VEGF-C and VEGF-D inhibitor)
    - Sozinibercept (OPT-302)

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Thank you

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