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Beyond VEGF

Understanding Blood-Retinal Barrier Biology and Emerging Mechanisms in DME and Neovascular AMD



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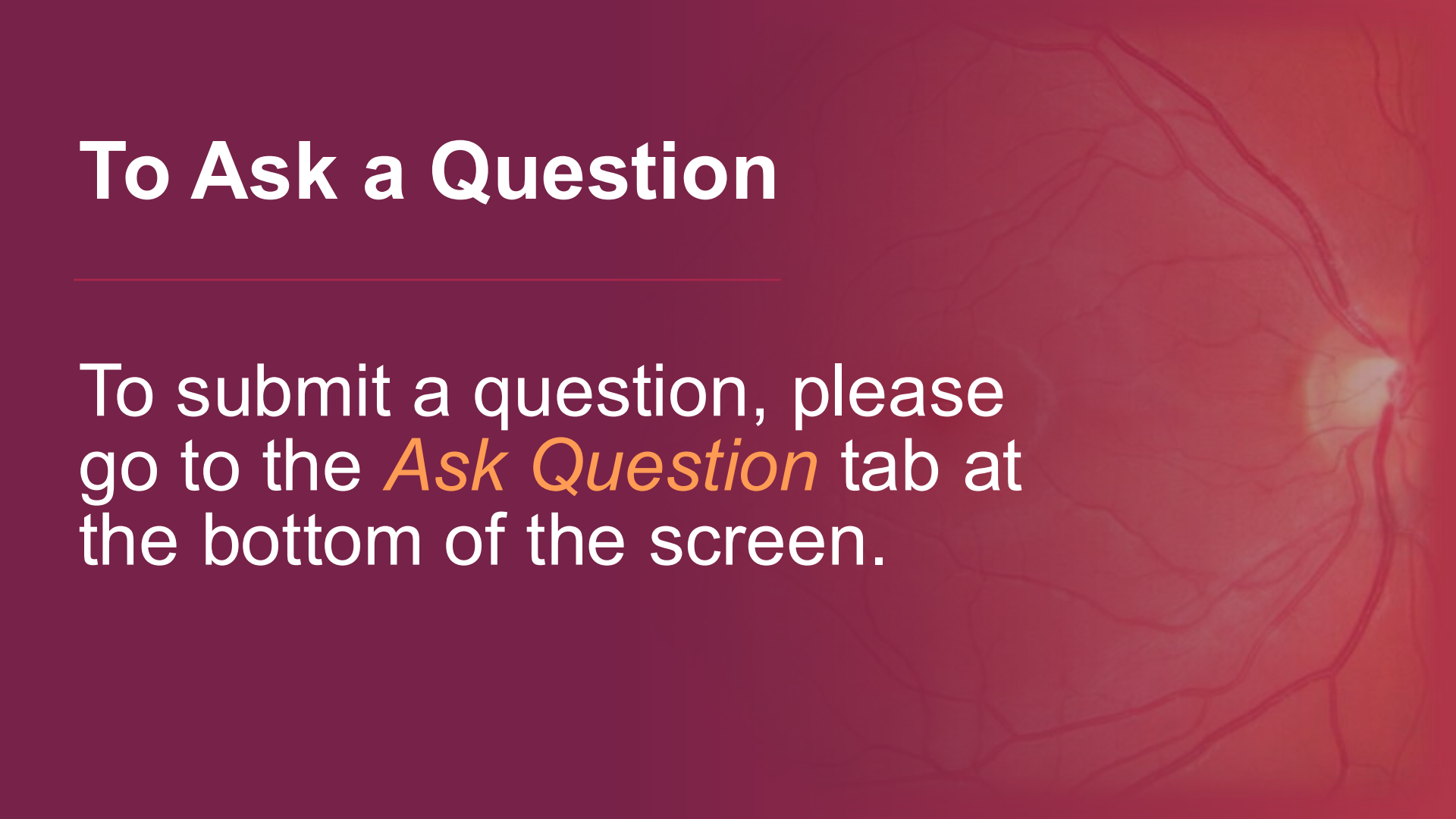
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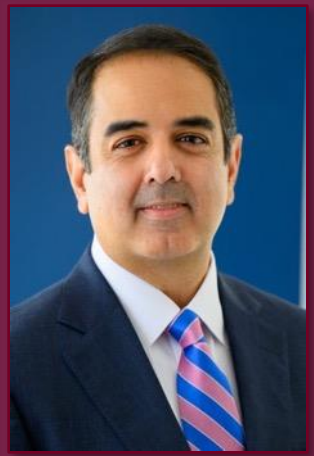
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Advisory Board—EyePoint Pharmaceuticals Inc.; and Ollin Biosciences, Inc.

Consultant—AbbVie Inc.; Alcon Inc.; Apellis Pharmaceuticals; Astellas Pharma Inc./Iveric Bio, Inc.; Bausch + Lomb; Carl Zeiss Meditec AG; Genentech, Inc./Roche; Harrow; Ocular Therapeutix, Inc.; Regeneron Pharmaceuticals Inc.; and Topcon Healthcare, Inc.

Consultant (ended)—EyePoint Pharmaceuticals Inc.; and Boehringer Ingelheim

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Stock Shareholder (ownership interest)—4D Molecular Therapeutics (4DMT); AbbVie Inc.; Adverum Biotechnologies, Inc.; Alcon; Aviceda Therapeutics; EyePoint Inc.; ForwardVue Pharma; INGENIA Therapeutics; KYS Vision, Inc.; Nanoscope Therapeutics, Inc.; Novartis Pharmaceuticals Corporation; Nvasc, Inc.; Ocular Therapeutix, Inc.; PulseMedica; Regeneron Pharmaceuticals Inc.; Replenish, Inc.; and Re-Vana Therapeutics

Other financial or material support—Patents/royalties: Replenish, Inc.

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All identified conflicts of interest have been mitigated.

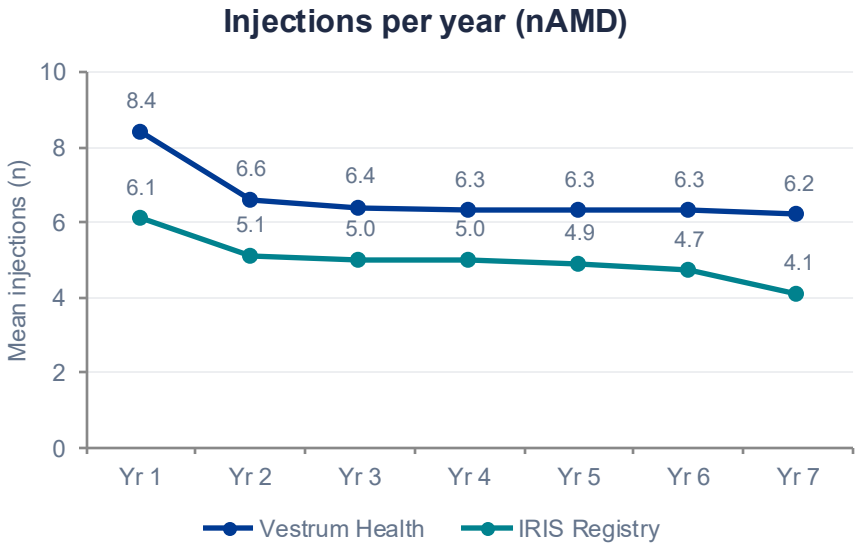
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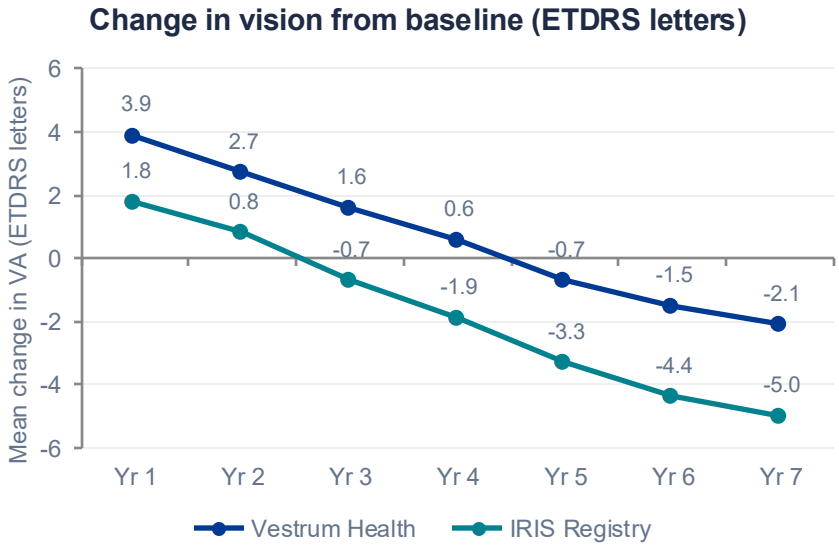
LEARNING OBJECTIVES

1. Evaluate the cellular and molecular mechanisms by which BRB breakdown drives vascular leakage and vision loss in DME and nAMD
2. Assess the mechanistic rationale for emerging therapeutic approaches targeting BRB stability and vascular regulation in DME and nAMD
3. Identify patients with DME or nAMD who demonstrate suboptimal anti-VEGF response to inform timely evidence-based management strategies

Real World Vision Loss with Current Standard of Care

Current Anti-VEGF Therapies Do Not Preserve Vision Long Term in Individuals with nAMD





In the real world, injections taper off over time, and vision drifts down with them

ETDRS = early treatment diabetic retinopathy study; nAMD = neovascular age-related macular degeneration.

Bressler SB, et al. *JAMA Ophthalmol*. 2016;134(3):278-285. Khanani AM, et al. *Ophthalmol Retina*. 2020;4(2):122-133. Moshfeghi AA, et al. *Invest Ophthalmol Vis Sci*. 2026;67(7):5268. Weng CY, et al. *Invest Ophthalmol Vis Sci*. 2026;67(7):5267.

Why the Gap Persists

NOT ENOUGH DRUG

Exposure falls away between injections, and the interval actually delivered in clinic is rarely the interval that was intended.

WRONG TARGET

VEGF-A is one input into a barrier that has several. Removing the ligand does not rebuild the junctions that were opened.

TOO LATE

Once the inner retina, the ellipsoid zone or the photoreceptors are structurally lost, drying the retina cannot recover the vision.

Different triggers, same result

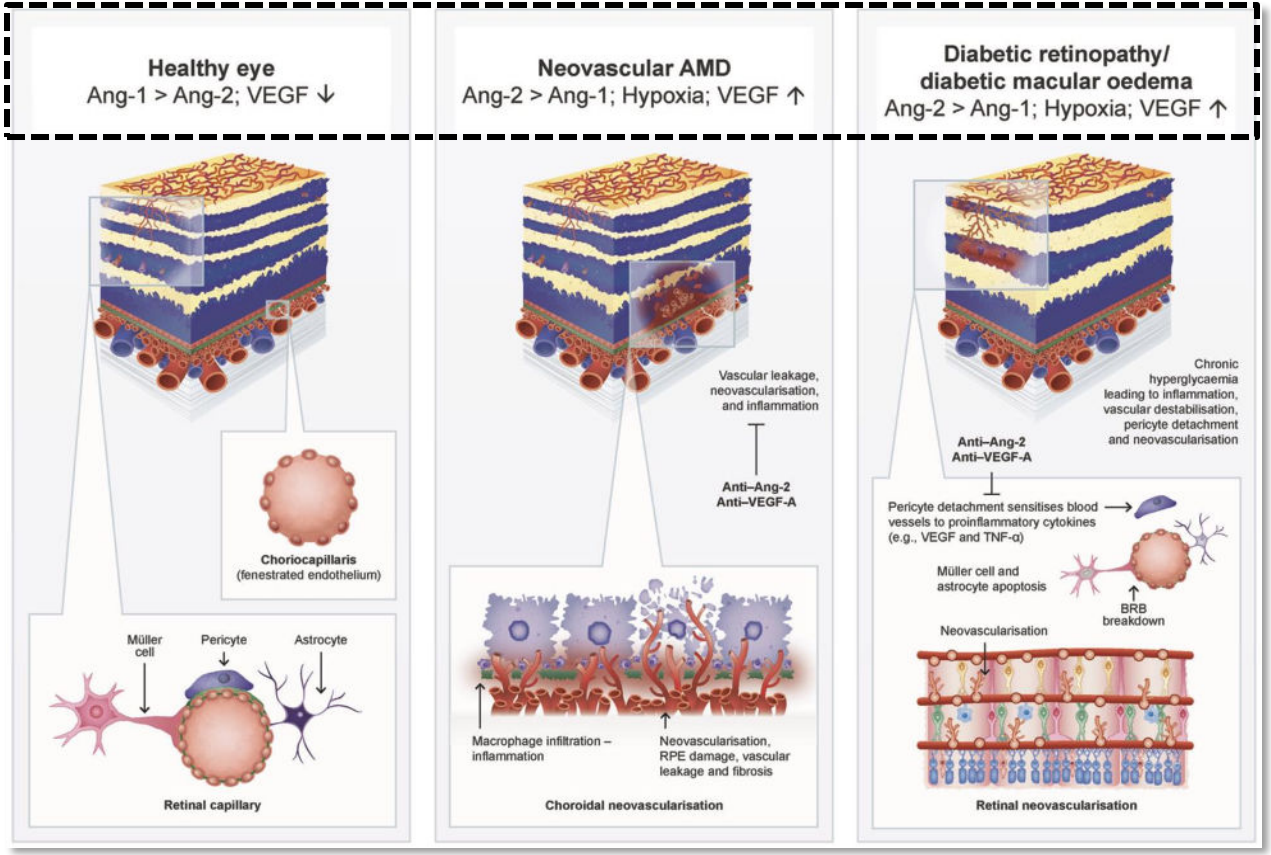
Healthy eye: Ang-1 outweighs Ang-2, VEGF low, barrier closed.

nAMD: Outer retinal blood retinal barrier disrupted

DME: Inner retinal blood retinal barrier disrupted

In both diseases **Ang-2** *overtakes* **Ang-1**, VEGF rises, and the barrier opens.

Barrier failure is multifactorial; anti-VEGF addresses one input.



AMD = age-related macular degeneration; Ang = angiopoietin; BRB = blood-retinal barrier; DME = diabetic macular edema; nAMD = neovascular age-related macular degeneration; RPE = retinal pigment epithelium; TNF-α = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor; VEGF-A = vascular endothelial growth factor A.

Bressler SB, et al. *JAMA Ophthalmol*. 2016;134(3):278-285. Joussen AM, et al. *Eye (Lond)*. 2021;35(5):1305-1316. Khanani AM, et al. *Ophthalmol Retina*. 2020;4(2):122-133.

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LEARNING OBJECTIVE

1

Evaluate the cellular and molecular mechanisms by which BRB breakdown drives vascular leakage and vision loss in DME and nAMD

Audience Response



Which statement best describes the primary role of the blood-retinal barrier?

A. It supplies oxygen and nutrients to the outer retina through the choroidal circulation
B. It selectively regulates what passes between the circulation and the neural retina
C. It filters metabolic waste products out of the vitreous
D. It pumps fluid out of the subretinal space through the retinal pigment epithelium
E. I'm not sure

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Patient Case: John



67-year-old man, 14 years type 2 diabetes, HbA1c 8.4%, blood pressure controlled on an ACE inhibitor.

Referred for reduced reading vision in the right eye over 4 months.

Bilateral center-involved DME. No prior intravitreal therapy at presentation.

No PDR. No vitreomacular traction. No epiretinal membrane.

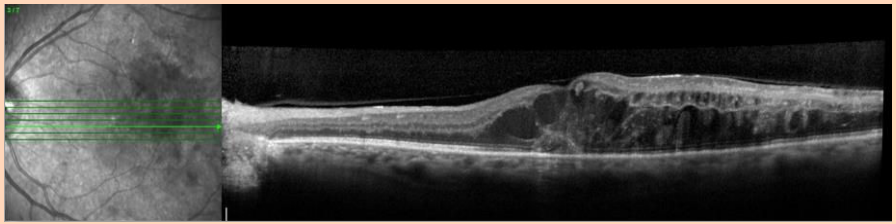


Figure from ASRS 2026 'Beyond Anti-VEGF' symposium

OD: BCVA 20/60, central subfield thickness **490 µm**, diffuse intraretinal cysts with early DRIL.

OS: BCVA 20/30, CST 334 µm.

ACE = angiotensin-converting enzyme; BCVA = best-corrected visual acuity; CST = central subfield thickness; DRIL = disorganization of the retinal inner layers; HbA1c = glycated hemoglobin; OCT = optical coherence tomography; OD = right eye; OS = left eye; PDR = proliferative diabetic retinopathy.

Patient Case: John



Three monthly **bevacizumab 1.25 mg**, then three monthly **aflibercept 2 mg** injections.

Switched to aflibercept at month 3 for **lack of response**. No inflammation or other AEs.

Injections received: 6 of 6 scheduled. Adherent. No missed visits.

OD at month 7: BCVA **20/50**, CST **442 µm**, improved from 20/60 and 487 µm, but persistent **center-involving macular edema**.

Fewer than 5 letters gained, and <10% thickness reduction.

He is adherent, he is treated, and he is not dry. What is the next decision and what would you need to know to make it?

AEs = adverse events.

Audience Response



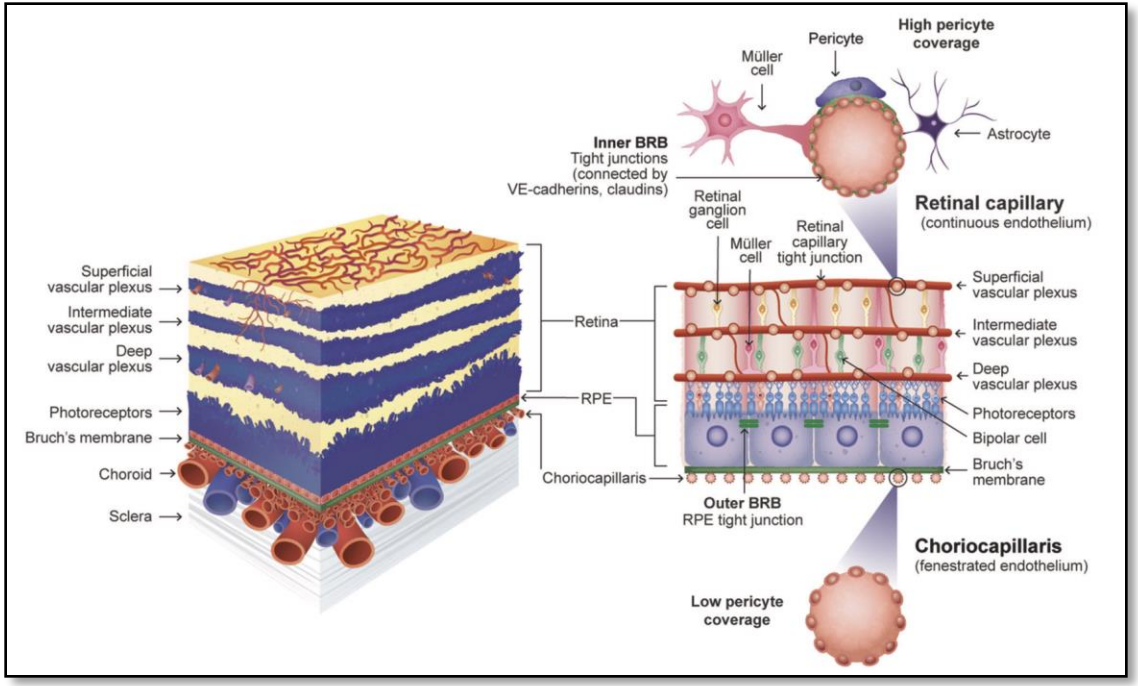
John is adherent and on schedule (six injections across two anti-VEGF agents) and still has center-involving edema at month 7. Which best explains it?

A. Not enough drug: exposure between injections is still inadequate
B. Wrong target: signals other than VEGF-A are holding the barrier open
C. Too late: structural change (DRIL, early photoreceptor loss) now limits recovery
D. I would need more information before choosing

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The Barrier Is Not Just the Vessel Wall

Three cell types work as one unit around every retinal capillary, and there is a second barrier at the RPE



1 Endothelial cells
Sealed to each other by tight junctions (claudin-5, occludin, ZO-1). The seal is actively maintained: it can be switched off, and switched back on.

2 Pericytes
Wrap the capillary more densely here than anywhere else in the body. They send the 'stay quiet' signal (Ang-1) to the endothelium. Losing them is the earliest lesion of diabetic retinopathy.

3 Müller glia and astrocytes
Their end-feet hug the vessel. They supply the barrier's maintenance signal (Norrin), clear water and potassium, and, when stressed, become a major source of VEGF.

4 Outer barrier: RPE
The tight junctions of the RPE. This is the barrier that fails in nAMD, and in the outer-retinal part of DME.

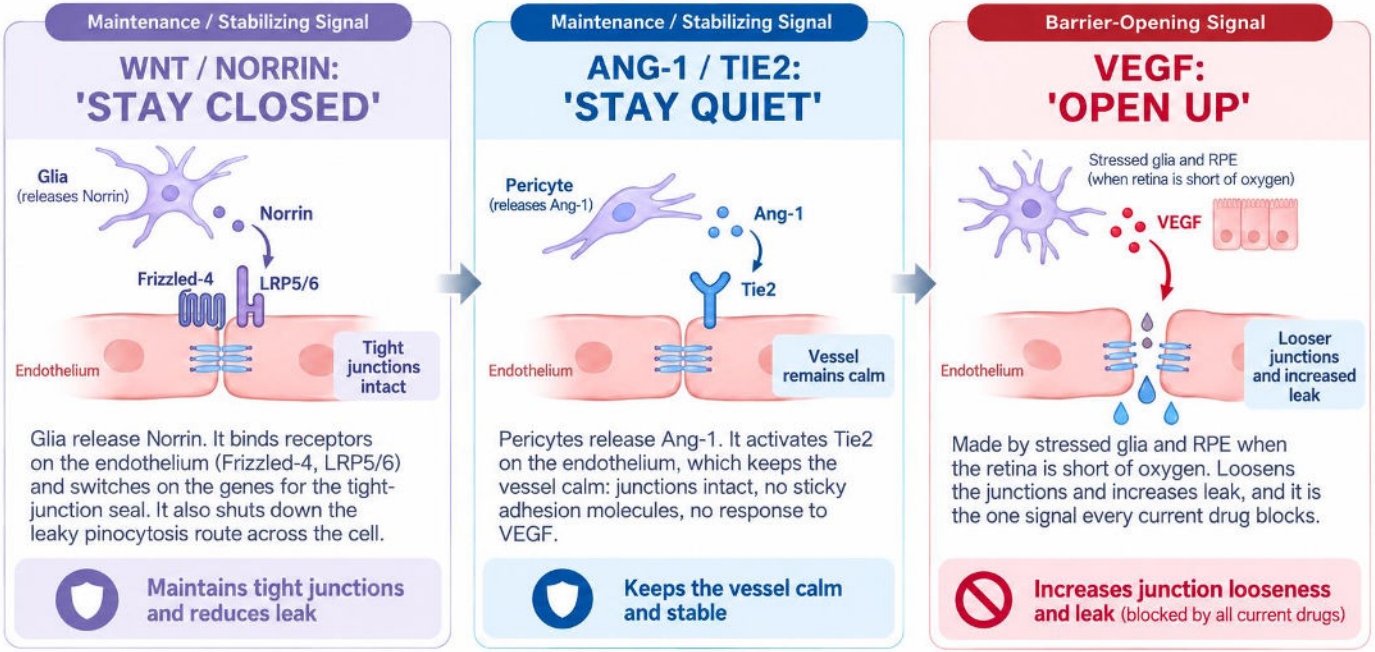
Key idea: the BRB is a cellular team, not the endothelial cell alone.

BRB = blood-retinal barrier; RPE = retinal pigment epithelium; ZO-1 = zonula occludens-1.

Díaz-Coránguez M, et al. *Vision Res.* 2017;139:123-137. Hammes HP, et al. *Diabetes.* 2002;51(10):3107-3112. Joussen AM, et al. *Eye (Lond).* 2021;35(5):1305-1316. Klaassen I, et al. *Prog Retin Eye Res.* 2013;34:19-48.

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Key Factors that Aid in BRB Seal Maintenance



Antonetti DA, et al. *Nat Rev Endocrinol*. 2021;17(4):195-206. Bora K, et al. *Cells*. 2023;12(20):2443. Saharinen P, et al. *Nat Rev Drug Discov*. 2017;16:635-661. Wang Y, et al. *Cell*. 2012;151:1332-1344.

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VEGF-A Opens the Junctions — the Mechanism You Already Treat

How VEGF-A opens the junction

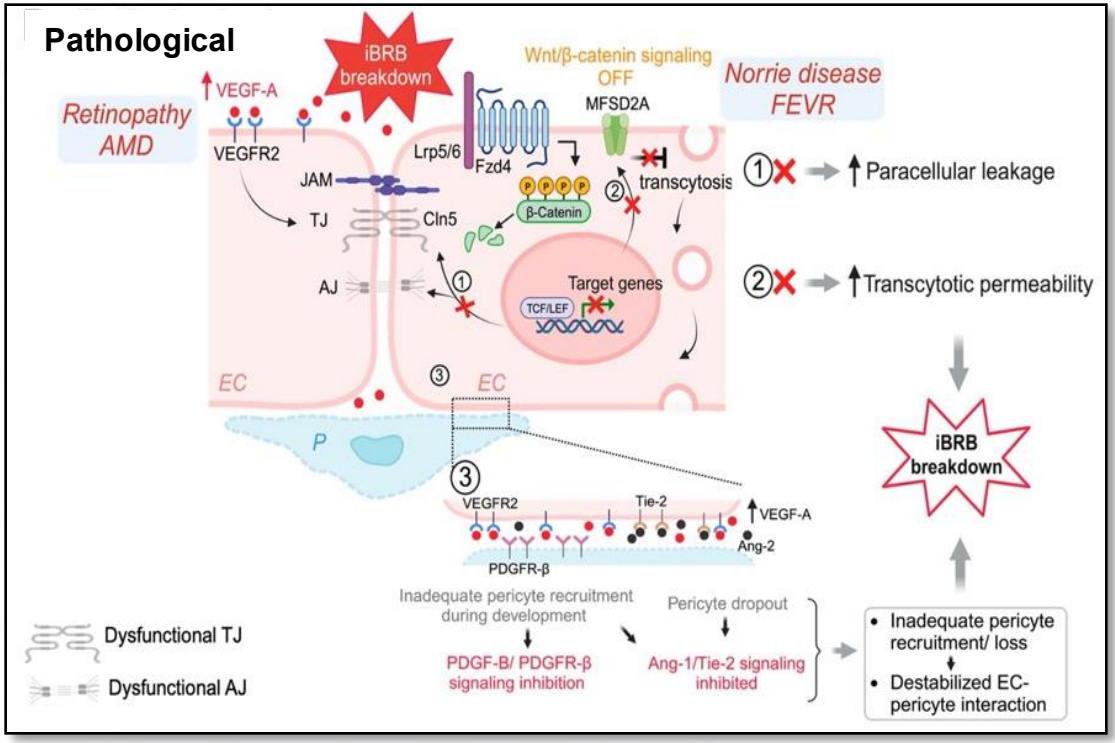
1 Trigger
- Hypoxia + hyperglycemia → VEGF-A expression
- VEGF-A binds VEGFR-2 on retinal endothelium

2 Junctional signaling
- PKC-β, Src-family kinases, and eNOS phosphorylate junctional proteins
- Proteins are driven off the membrane

3 Clinical leak
- The junction opens → fluid + protein enter the retina
- This is the leak seen on OCT

What anti-VEGF does
Removes the ligand and stops the signal actively prying the junction open.

What it does not restore
- Claudin-5 expression
- Lost pericyte coverage
- The stabilizing signal that holds the junction shut



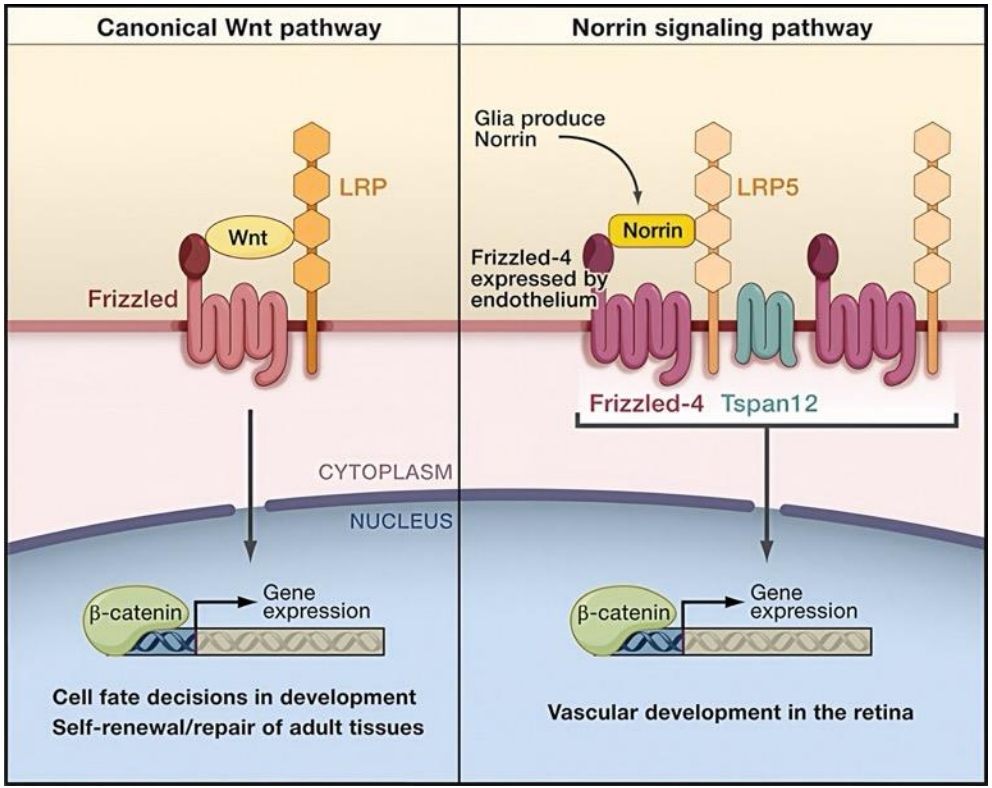
This is the gap: anti-VEGF suppresses the opening signal, but it ***does not rebuild the barrier.***

AJ = adherens junction; Ang = angiopoietin; BRB = blood-retinal barrier; Cln5 = claudin-5; EC = endothelial cell; eNOS = endothelial nitric oxide synthase; FEVR = familial exudative vitreoretinopathy; Fzd4 = frizzled-4; iBRB = inner blood-retinal barrier; JAM = junctional adhesion molecule; Lrp5/6 = low-density lipoprotein receptor-related protein 5/6; MFSD2A = major facilitator superfamily domain-containing protein 2A; P = pericyte; PDGF-B = platelet-derived growth factor B; PDGFR-β = platelet-derived growth factor receptor beta; PKC-β = protein kinase C beta; TCF/LEF = T-cell factor/lymphoid enhancer factor; Tie = tyrosine kinase with immunoglobulin-like and EGF-like domains; TJ = tight junction; VEGF-A = vascular endothelial growth factor A; VEGFR2 = vascular endothelial growth factor receptor 2; Wnt = wingless-related integration site; ZO-1 = zonula occludens-1. Antonetti DA, et al. *N Engl J Med*. 2012;366(13):1227-1239. Campochiaro PA. *Prog Retin Eye Res*. 2015;49:67-81.

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Wnt/β-Catenin: The Maintenance Program

Norrin is the retina's own barrier-repair signal: glia make it, the endothelium reads it, and the seal depends on it



1 HOW IT WORKS

Norrin from glia binds **Frizzled-4** on the endothelium.

β-catenin is protected from breakdown, moves to the nucleus, and switches on **claudin-5,** while shutting down the leaky route.

When this pathway is absent, retinal vessels are immature and leaky (eg, Norrie disease, FEVR).

KEY PATHWAY COMPONENTS			
	Norrin	Frizzled-4	LRP5
	TSPAN12	β-catenin	claudin-5

2 WHAT GOES WRONG IN DME

High glucose and **VEGF** turn this signal down, so the seal genes fade.

In laboratory models, re-supplying **Norrin** reverses VEGF-induced leak and rebuilds **claudin-5.**

This shows the barrier can be **repaired,** not just protected.

3 WHY IT MATTERS

This is a **'stay closed'** maintenance pathway that no approved drug directly targets.

It provides the biologic rationale for **Wnt-pathway agonists** now in trials.

Status: investigational.

LRP = low-density lipoprotein receptor-related protein; LRP5 = low-density lipoprotein receptor-related protein 5; TSPAN12 = tetraspanin 12

Bora K, et al. *Cells*. 2023;12(20):2443. Clevers H. et al. *Cell*. 2009;139(2):227-229. Díaz-Coránguez M, et al. *J Biol Chem*. 2020;295(14):4647-4660. Junge HJ, et al. *Cell*. 2009;139(2):299-311. Wang Y, et al. *Cell*. 2012;151:1332-1344. Xu Q, et al. *Cell*. 2004;116(6):883-895.

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Angiopoietin–Tie2 Axis: Maintenance Program

When Tie2 is active



- The vessel is quiescent
- Junctions tight, leukocytes not adherent
- VEGF responses damped

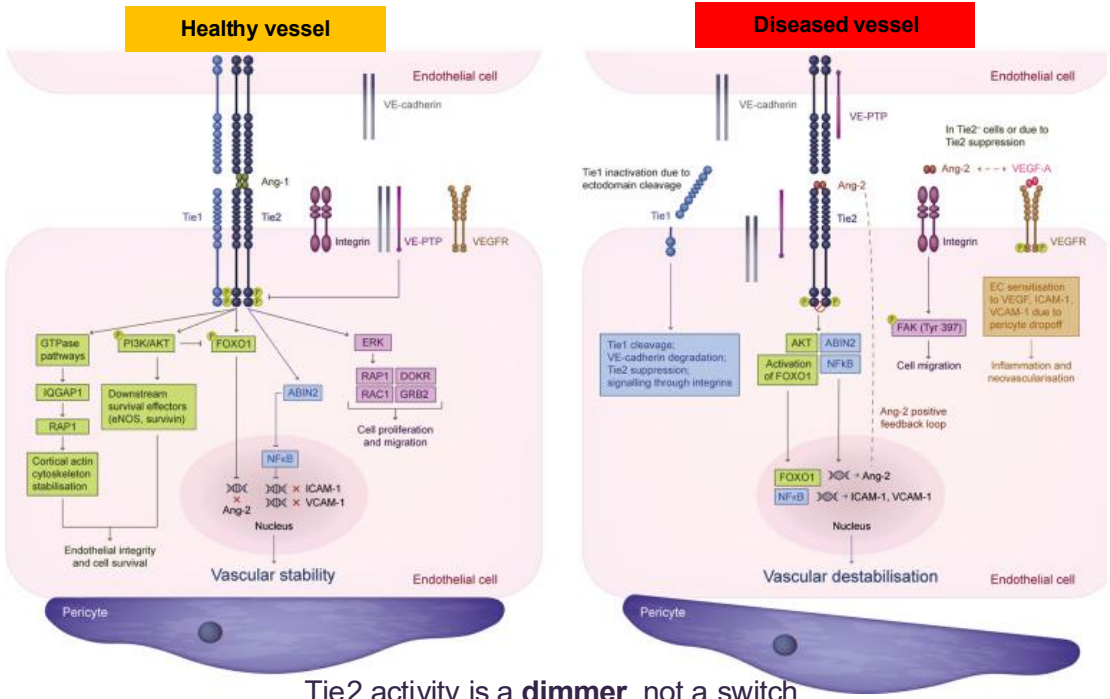
Angiopoietin-1 (Ang-1) — Released by pericytes, is the Tie2 **agonist** — it keeps the receptor on.

Angiopoietin-2 (Ang-2) — Stored in endothelial Weibel–Palade bodies and released on stress, is a context-dependent **antagonist** — it competes Ang-1 off and switches the receptor down.

VE-PTP — A phosphatase, dephosphorylates Tie2 and further reduces signaling.

Clinical insight

Ang-2 is elevated in the vitreous of eyes with DME and with nAMD, and rises alongside VEGF.



Tie2 activity is a **dimmer**, not a switch

Ang-1 pericyte-derived agonist	Ang-2 Weibel–Palade, stress-released	VE-PTP phosphatase

◀ Tie2 active · vessel quiescent — Tie2 down · vessel destabilized ▶

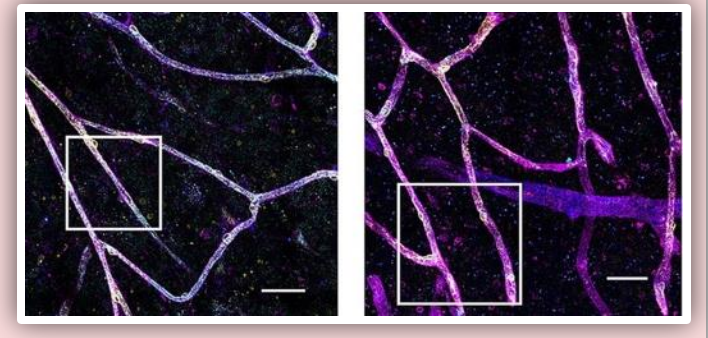
Tie2 = tyrosine kinase with immunoglobulin-like and EGF-like domains 2; VE-PTP = vascular endothelial protein tyrosine phosphatase.

Joussen AM, et al. *Eye (Lond)*. 2021;35(5):1305-1316. Regula JT, et al. *EMBO Mol Med*. 2016;8(11):1265-1288. Saharinen P, et al. *Nat Rev Drug Discov*. 2017;16(9):635-661.

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Other Hands on the Barrier

Contributors beyond VEGF-A that vary by disease



Control | **Diabetic retinopathy**

- Pericyte loss in human diabetic retina.
- Pericyte markers (yellow/cyan) thin out along the capillary basement membrane (magenta)
- Pericyte density fell from **~7 to ~4 per mm of capillary.**

PDGF-B

DME & DR

- The signal that keeps pericytes attached. High glucose blunts it → pericytes die → the Ang-1 supply is lost.

Semaphorin 3A

DME & RVO

- Released by oxygen-starved nerve cells.
- Directly increases leak and stops new vessels from re-growing into ischemic retina.

Complement

nAMD & DR

- Local immune activation on the RPE and choroid.
- Dominant in AMD; adds to inflammation in DR.

Inflammatory cytokines

DME > nAMD

- IL-6, IL-8, MCP-1, ICAM-1: microglia switch on and white cells stick to the vessel wall.
- Stay high in non-responders; show up as bright dots on OCT.

Müller glia

DME & RVO

- Swell when their water and potassium channels are mislocated; stressed glia become a major VEGF source and stop making Norrin.

PIGF / VEGF-B

DME

- Cousins of VEGF that recruit monocytes and amplify VEGF.

DR = diabetic retinopathy; ICAM-1 = intercellular adhesion molecule 1; IL = interleukin; MCP-1 = monocyte chemoattractant protein 1; PIGF = placental growth factor; RVO = retinal vein occlusion; VEGF-B = vascular endothelial growth factor B. Bai Y, et al. *J Pathol*. 2009;219(4):446-454. Bakker-van Bugnum N, et al. *Front Neurosci*. 2026;20:1749112. Cerani A, et al. *Cell Metab*. 2013;18(4):505-518. Geraldes P, et al. *Nat Med*. 2009;15(11):1298-1306. Rübsam A, et al. *Int J Mol Sci*. 2018;19(4):942. Pannicke T, et al. *Diabetes*. 2006;55(3):633-639.

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LEARNING OBJECTIVE

2

Assess the mechanistic rationale for emerging therapeutic approaches targeting BRB stability and vascular regulation in DME and nAMD



Audience Response



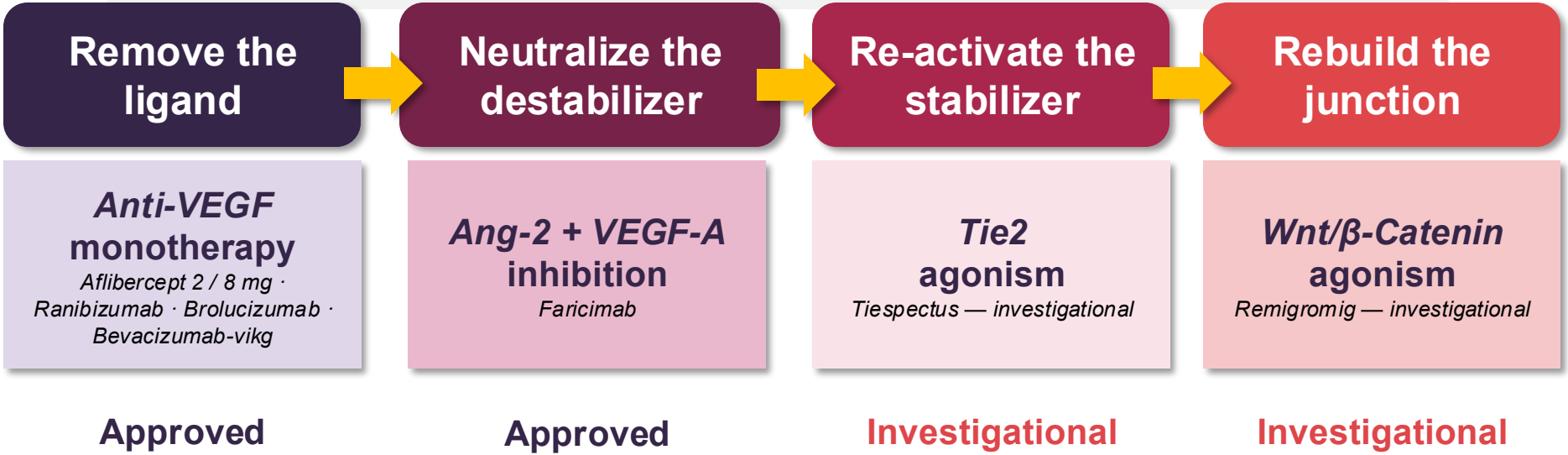
A direct Tie2 agonist is designed to:

A. Neutralize VEGF-A so that Tie2 signaling can recover on its own
B. Neutralize angiopoietin-2 so that endogenous angiopoietin-1 can re-activate Tie2
C. Activate the Tie2 receptor directly, independent of how much angiopoietin-1 is available
D. Inhibit Tie2 kinase activity to limit abnormal vessel growth
E. I'm not sure

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A Map of the Treatment Landscape Along the Barrier Plane

Where each approach acts on barrier leakage: left to right, increasingly proximal to the barrier itself



Blocking the Destabilizer vs. Activating the Stabilizer

	Ang-2 neutralization + VEGF-A (Faricimab - Approved)	Direct Tie2 agonism + VEGF inhibition (Tiespectus - Investigational)
Point of attack	Removes the ligand that blocks Tie2	Activates the Tie2 receptor itself
Depends on endogenous Ang-1?	Yes: Tie2 is re-activated only if Ang-1 is available	Designed not to: the antibody supplies the activating signal
Pericyte-depleted diabetic vessel	Ang-1 supply may be reduced	Rationale for the approach; clinical relevance unproven
Clinical evidence	Phase 3 in DME and nAMD (YOSEMITE/RHINE, TENAYA/LUCERNE); approved 2022	Phase 1/2a (RIOJA); pivotal trials in nAMD and DME ongoing

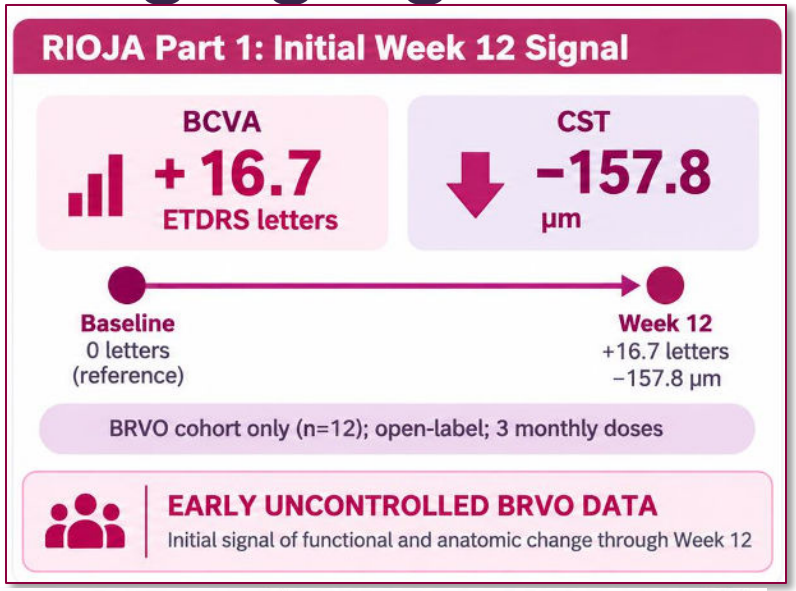
Same pathway, different point of attack. No head-to-head data exist; mechanism is not evidence of superiority.

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ClinicalTrials.gov. Identifier: NCT06664502, Joussen AM, et al. *Eye (Lond)*. 2021;35(5):1305-1316. Regula JT, et al. *EMBO Mol Med*. 2016;8(11):1265-1288. Saharinen P, et al. *Nat Rev Drug Discov*. 2017;16(9):635-661.

Direct Tie2 Agonism: Emerging Agent

- **Mechanistic distinction:** direct Tie2 agonism is designed to activate the stabilizing endothelial receptor rather than neutralize Ang-2 and depend on endogenous Ang-1.
- **Tiespectus** is an investigational bispecific antibody designed to activate Tie2 and inhibit VEGF.
- **RIOJA Phase 1/2a (NCT06664502), BRVO cohort:** open-label dose-escalation in **12 treatment-naïve eyes**; 1, 4, 7, or 10 mg Q4W for three doses.
- **Observed at Week 12:** mean BCVA change **+16.7 ETDRS letters**; mean CST change **−157.8 µm**.
- **Safety reporting:** all dose levels well tolerated; no rescue therapy, intraocular inflammation, or retinal vasculitis reported during the 12-week primary period.



Ongoing randomized studies — Part 2 DME and wet AMD cohorts pending

MALBEC (NCT07440225)

- Randomized, double-masked Phase 2b/3 treatment-naïve **nAMD** study; two Tiespectus regimens versus aflibercept 2 mg; primary endpoint mean BCVA change at Year 1.

TORRONTES (NCT07496567)

- Randomized, double-masked Phase 2b/3 treatment-naïve **nAMD** study; two Tiespectus regimens versus aflibercept 2 mg; primary endpoint mean BCVA change at Year 1.

SANGIOVESE (NCT07705555)

- Randomized, Double-Masked, Multicenter, 3-Arm, Pivotal Phase 3 Study to Evaluate the Efficacy and Safety of IVT Tiespectus Compared with Aflibercept (2 mg) in Participants with **DME**

SYRAH (NCT07705607)

- Randomized, Double-Masked, Multicenter, 3-Arm, Pivotal Phase 3 Study to Evaluate the Efficacy and Safety of IVT Tiespectus Compared with Aflibercept (2 mg) in Participants with **DME**

BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CST = central subfield thickness; IVT = intravitreal.

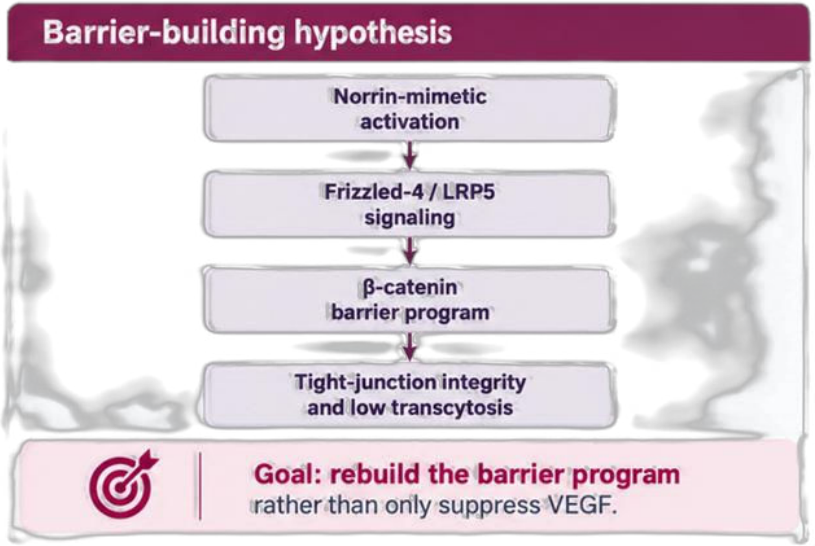
ClinicalTrials.gov. Identifiers: NCT06664502, NCT07440225, NCT07496567, NCT07705555, and NCT07705607. Jo G, et al. *Nat Commun*. 2021;12(1):6287; Gallagher J. Retinal Physician Website. 2026. https://www.retinalphysician.com/issues/2026/asrs/early-tiespectus-data.

Wnt/Norrin Pathway Agonism: Emerging Agent

- **Wnt/Norrin signaling** supports retinal endothelial barrier identity, including transcriptional programs associated with tight-junction integrity and low transcytosis.
- **Mechanistically distinct from VEGF suppression:** designed to engage a pathway involved in maintaining the endothelial barrier program.
- **Remigromig** is an investigational tetravalent antibody designed to activate Frizzled-4/LRP5 signaling in a Norrin-mimetic manner.

BRUNELLO Trial (Year 1 results): both doses *non-inferior* to control

	Remigromig		Ranibizumab
Year 1 outcome	**0.5 mg**	**0.8 mg**	**0.5 mg (control)**
BCVA gain, letters (p-value*)	**+9.1** (0.0129)	**+8.7** (0.0222)	**+11.8**
PDR AEs	6.7%	6.1%	0.9%



Clinical trials in development

BRUNELLO (NCT06571045) (Phase 2/3)
Randomized, double masked pivotal study to evaluate the efficacy and safety of 2 dose levels of remigromig in comparison with the active control, ranibizumab, in patients with **DME**

BAROLO (NCT06957080) (Phase 2/3)
Randomized, double masked pivotal study to evaluate the efficacy and safety of 2 dose levels of remigromig in comparison with the active control, ranibizumab, in patients with **DME**

Super Tuscan (NCT07205887) (Phase 2)
Randomized, dose-masked study of intravitreal remigromig in participants with **nAMD** or **macular edema** due to **BRVO**

*Multiplicity-adjusted. ClinicalTrials.gov. Identifiers: NCT06571045, NCT06957080, and NCT07205887. Yemanyi F, et al. *Int J Mol Sci*. 2021;22(21):11877. D'Amico D. American Academy of Ophthalmology (AAO) Annual Meeting. 2026.

Mechanistic Comparison Matrix

Approach	Molecular Target	Status	What it leaves unaddressed	Where the rationale is strongest
Anti-VEGF monotherapy	**VEGF-A (± PlGF/VEGF-B with aflibercept)**	• **Approved**	• Ang-2/Tie2 pathway • Wnt program • Pericyte loss • Chronic inflammation	VEGF-driven leak; most treatment-naive eyes
Dual Ang-2 / VEGF-A	**VEGF-A + Ang-2**	• **Approved**	• Wnt/Norrin structural pathways • Advanced fibrosis • Alternative inflammatory • cascades	Ischemic, Ang-2-high eyes
Tie2 agonism + VEGF	**Tie2 receptor + VEGF**	• **Investigational (Phase 2/3)**	• Wnt junction program • Non-endothelial neural pathologies • Ischemic vasorepulsion cues	Pericyte-depleted vessels with little Ang-1
Wnt/Norrin agonism	**FZD4/LRP5**	• **Investigational (Phase 2/3)**	• No direct VEGF blockade • DR-progression signal under study	Loss of the barrier maintenance program
Corticosteroid; Sema3A/Nrp1	**Inflammatory cytokines; Sema3A**	• **Steroid implants approved (DME)** • **Sema3A early**	• Immediate anti-permeability mechanics of early VEGF leaks (Sema3A/Nrp1) • IOP and cataract risk (steroid)	Inflammation-high phenotype (many HRF)
Sustained delivery	**VEGF pathway (exposure)**	• **PDS approved** • **TKI implants investigational**	• Same biology as anti-VEGF	High burden or adherence risk

DR = diabetic retinopathy; HRF = hyperreflective foci; IOP = intraocular pressure; Nrp1 = neuropilin-1; PDS = Port Delivery System; PlGF = placental growth factor; Sema3A = semaphorin 3A; TKI = tyrosine kinase inhibitor; VEGF-B = vascular endothelial growth factor B.

ElSayed NA, et al. *Diabetes* Care. 2023;46(Supplement_1):S231-S243. Joussen AM, et al. *Eye (Lond)*. 2021;35(5):1305-1316. Martyka A, et al. *Surv Ophthalmol.* 2026;71(5):1396-1410. Sivaprasad S, et al. *Eye (Lond)*. 2025;39(18):3209-3217. Wykoff CC, et al. *Lancet*. 2022;399(10326):741-755.

LEARNING OBJECTIVE

3

Identify patients with DME or nAMD who demonstrate suboptimal anti-VEGF response to inform timely evidence-based management strategies

Patient Case: Carlos

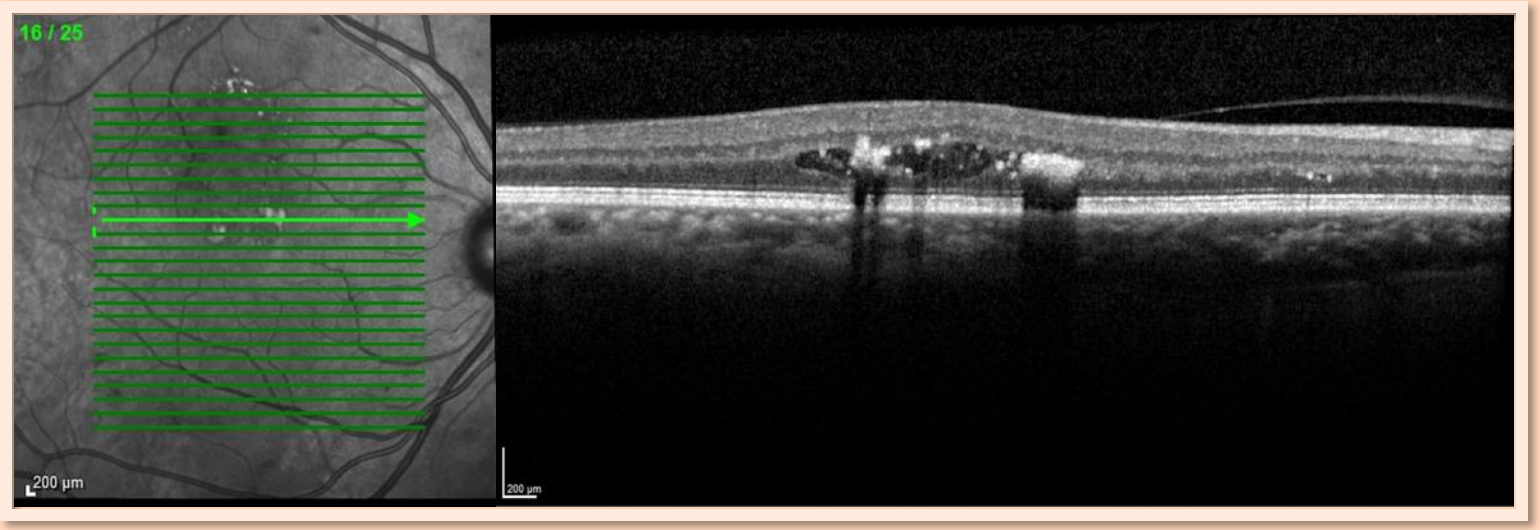


- **67-year-old Hispanic man**, type 2 diabetes. Mild blurred vision OD > OS over the past year. **VA 20/30− OD, 20/25 OS.** Center-involving **DME** on OCT.
- **Bevacizumab ×11, ranibizumab ×3, aflibercept ×4**: VA fell to **20/60** five weeks after the last aflibercept injection, edema persistent.
- **Faricimab ×4**: VA 20/40 — fluid reduced, not resolved.
- **Dexamethasone implant** added: VA 20/50 at six weeks.
- **Faricimab, continued to #10**: VA **20/60**, edema persists.
- **Three** anti-VEGF-A agents, **One** dual Ang-2/VEGF-A inhibition, and **One** corticosteroid, and the barrier is still open.

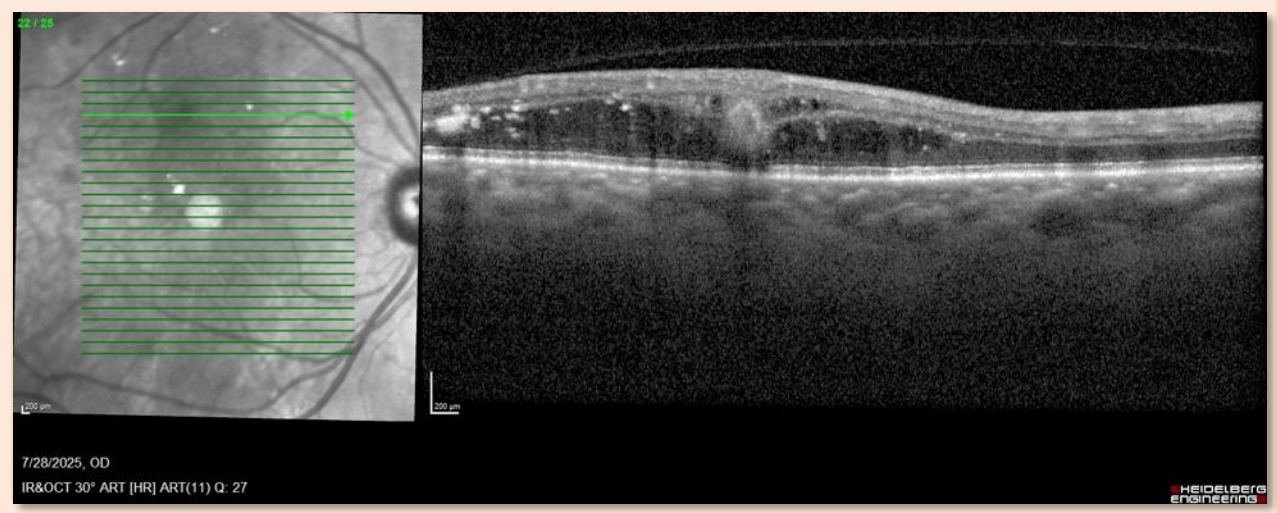
DME case: Baseline fluorescein angiography, both eyes — typical diabetic leakage, not a BRVO pattern

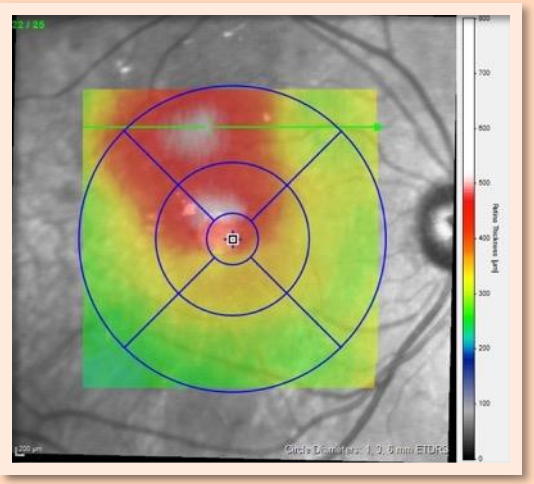


DME case contd: Baseline OCT — bevacizumab started

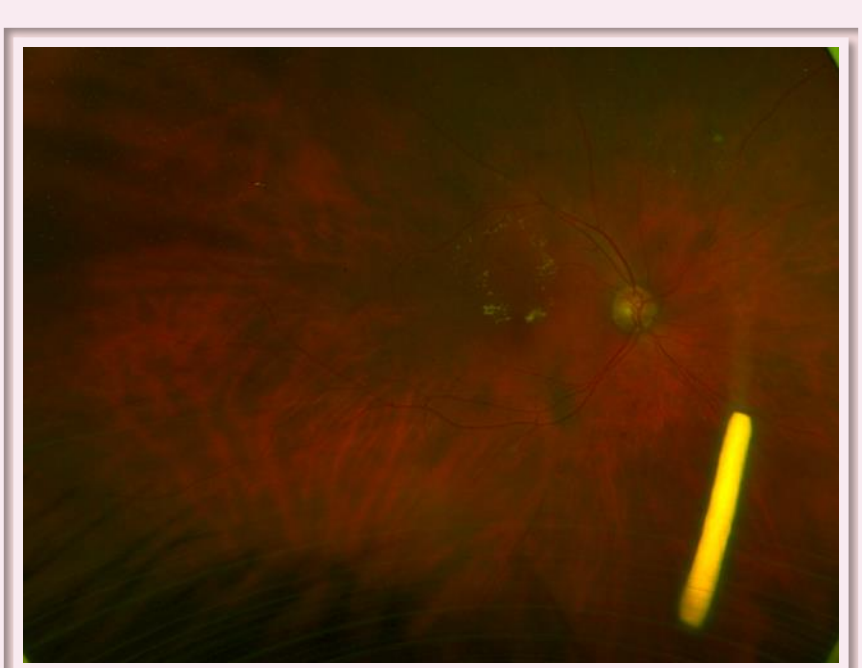


DME case contd: VA 20/60 after bevacizumab ×11, ranibizumab ×3, aflibercept ×4 — faricimab started

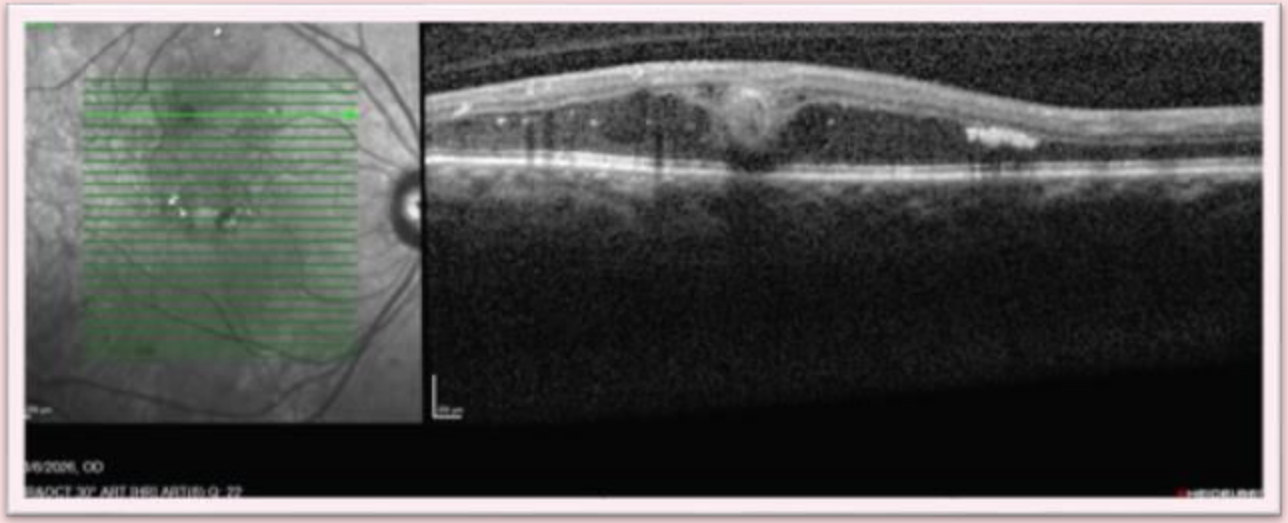


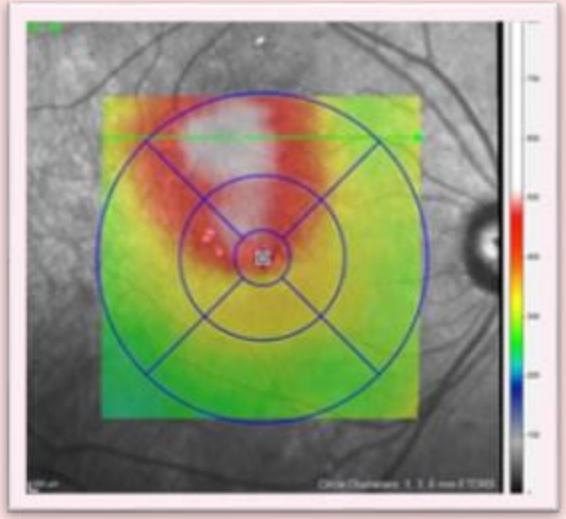


DME case contd: Color fundus after dexamethasone implant — implant visible posteriorly

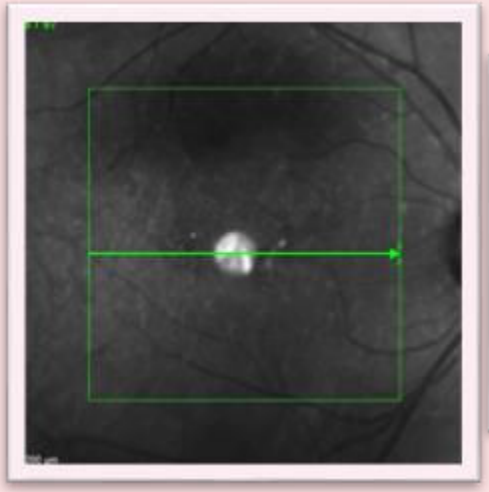


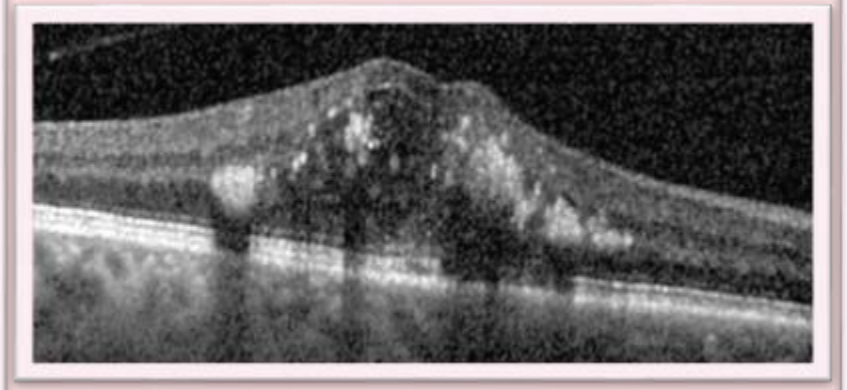
DME case contd: VA 20/50, 6 weeks after dexamethasone implant

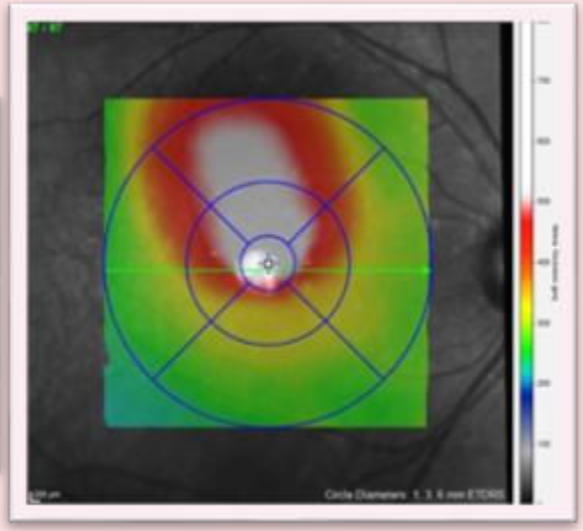




DME case contd: VA 20/60, 5 weeks after faricimab #10







CME OUTFITTERS

No Universal Definition — Faculty Commentary

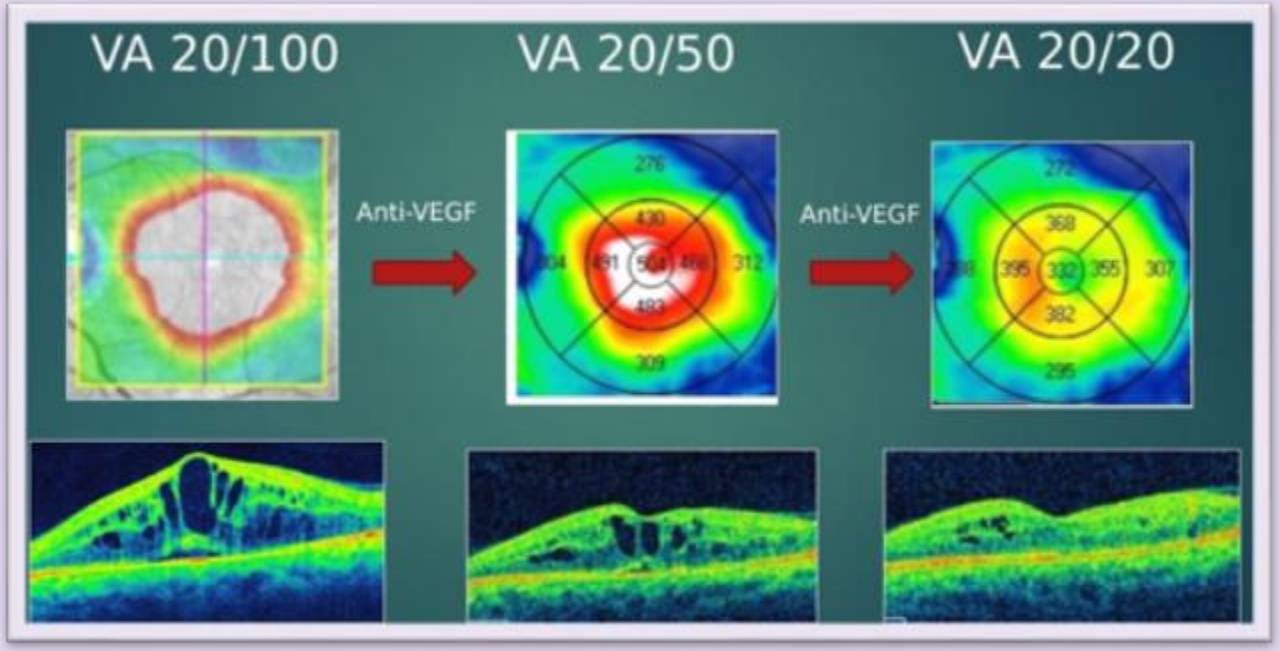
Response	Morphology	Functional
Good	• Absence of SRF, IRF, and IRC, or • Reduction in CRT greater than 75% from baseline	• Improvement in VA greater than 5 letters from baseline • In eyes with good starting VA (ETDRS 70 letters or above), a ceiling effect may limit functional gain • If VA is already good, pay closer attention to morphology
Partial	• Reduction in CRT of 25% to 75% from baseline, and/or • Persistence of SRF, IRF, or IRC, and/or • Appearance of new IRC, IRF, or SRF	• Change in VA of 1 to 5 letters from baseline
Poor	• Reduction in CRT of 0% to less than 25% from baseline, and/or • Persistence of SRF, IRF, or IRC, and/or • Appearance of new IRC, IRF, or SRF	• Change in VA of 0 to 4 letters from baseline
Non-response	• Unchanged or increasing CRT, SRF, IRF, and/or PED compared with baseline	• Decline in VA by more than 5 letters from baseline • Assess from 1 month after the third initiation injection

CRT = Central retinal thickness; IRC = Intraretinal cysts; IRF = Intraretinal fluid; PED = Pigment epithelial detachment; SRF = Subretinal fluid.

CME OUTFITTERS

Amoaku WM, et al. *Eye (Lond)*. 2015;29(6):721-731. Furino C, et al. *J Ophthalmol*. 2021;2021:6654168.

What a Good Response Looks Like



20/100 → 20/20

Vision over two anti-VEGF cycles

504 → 332 µm

Central subfield thickness

Cysts collapse

as the barrier re-seals; hard exudate lags behind

Figure from Dr. Singh's 'Innovations in Diabetic Retinopathy' lecture

OCT Biomarkers Reveal Where the Barrier is Failing

- OCT shows the footprint of barrier failure
- It can help explain response and set some expectations

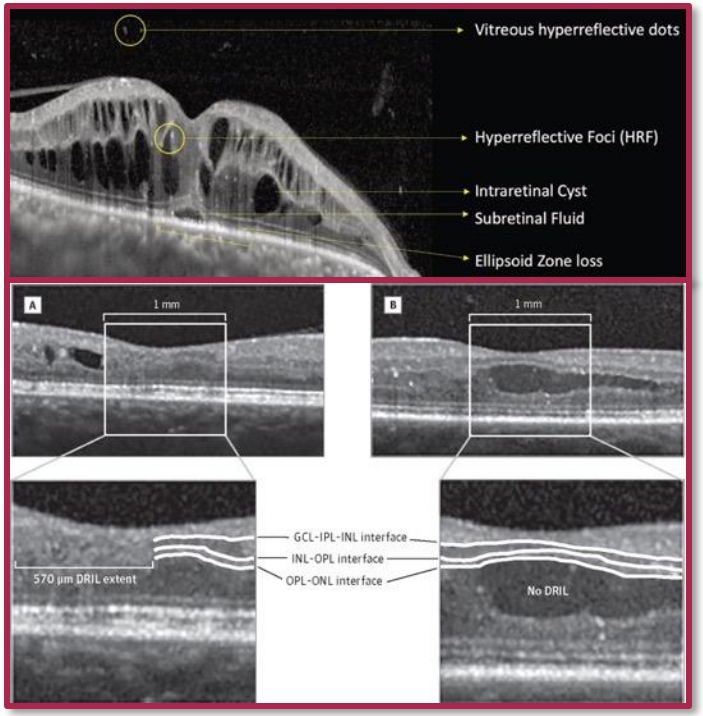
What the compartment implies

Intraretinal fluid
Inner BRB failure. Junctional leak from retinal capillaries; the dominant DME pattern.

Subretinal fluid
Outer BRB / RPE failure, or a barrier-incompetent neovascular complex; the dominant nAMD pattern.

Mixed IRF and SRF
Both barriers involved. Common in chronic disease and in incomplete responders.

Interpretation
Compartment is a mechanistic clue, not a diagnosis. Read it alongside the clinical picture.



What predicts a ceiling on recovery

DRIL
Disorganization of retinal inner layers. Associated with worse visual acuity outcomes independent of thickness.

EZ disruption
Photoreceptor integrity loss. Structural, and largely not recoverable by drying the retina.

Hyperreflective foci
Associated with inflammatory activity and with chronicity.

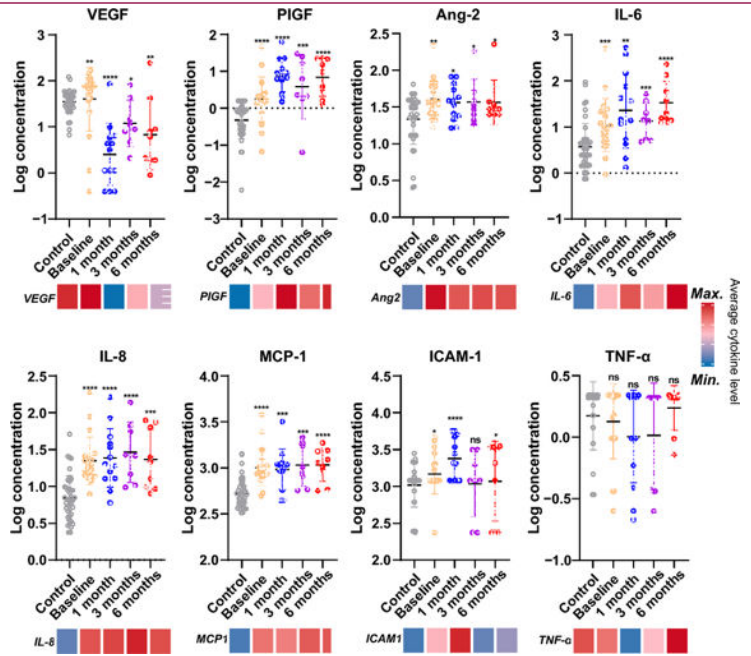
Why this matters
These findings help explain why an eye can dry and still not see — and why 'thickness normalized' is not the same as 'treated successfully'.

EZ = ellipsoid zone. Grewal DS. Retina Specialist Website. 2022. https://www.retina-specialist.com/article/oct-biomarkers-in-uveitis-an-update. Nanji K, et al. *Ophthalmology*. 2026;133(1):75-90. Sun JK, et al. *Diabetes*. 2015;64(7):2560-2570. Sun JK, et al. *JAMA Ophthalmol*. 2014;132(11):1309-1316.

CME OUTFITTERS

Non-Response Is Often the Wrong Target

In eyes that fail anti-VEGF, VEGF falls as expected, but the other barrier-opening signals stay high



Aqueous cytokines in anti-VEGF non-responders (n = 20) at baseline, 1, 3 and 6 months. VEGF drops after injection; PIGF, Ang-2, IL-6, IL-8 and MCP-1 remain elevated.

A 5-signal aqueous test (VEGF, Ang-2, IL-6, MCP-1, ICAM-1) separates responders from non-responders before the first injection.

BACK TO OUR PATIENT

- Six on-time injections across two drugs.
- Bright dots >20 in the inner retina, DRIL, thickness swinging ±58 µm across three visits, fluid still present.
- **VEGF is not what is holding this barrier open.**
- **Working hypothesis:**
  - **Ang-2 (the pericyte's 'stay quiet' signal is gone), a faded Wnt maintenance signal, and inflammation: targetable pathways, a reason to ask whether a seventh injection of the same class is the right next step.**

ICAM-1 = intercellular adhesion molecule-1; IL-6 = interleukin-6; MCP-1 = monocyte chemoattractant protein-1.

Yang F, et al. *Eye Vis (Lond)*. 2026;13(1):12. Ying J, et al. *Photodiagnosis Photodyn Ther*. 2025;55:104728.

CME OUTFITTERS

Patient Case: Phil



- **74-year-old man**, exudative AMD in the left eye at presentation: pigment epithelial detachment, subretinal fluid, and subretinal hyperreflective material. ERM with pseudohole OU; nuclear sclerosis and mild PSC OU. **VA 20/20 OD, 20/30 OS.**

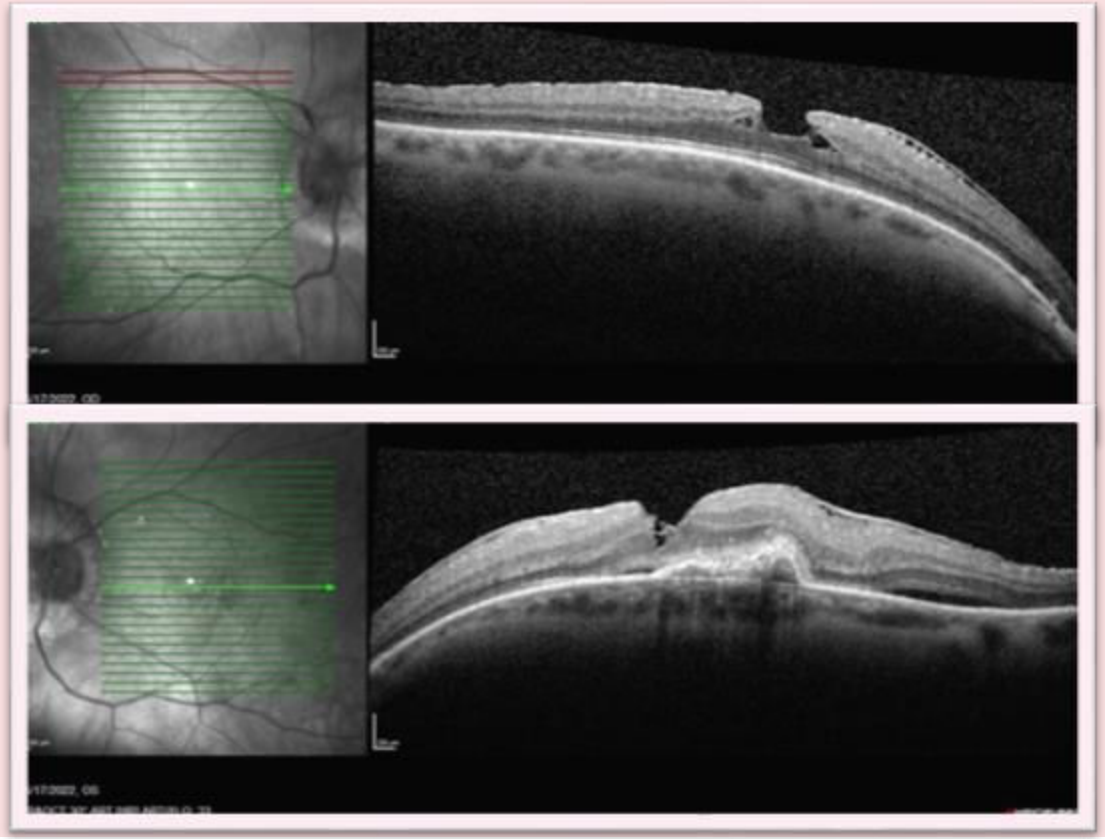
- **Ranibizumab ×7**, every 4–5 weeks: VA 20/30−, fluid persists.
- **Faricimab ×15**: fluid persists.
- **Aflibercept 8 mg ×18**, every 5 weeks: still wet.

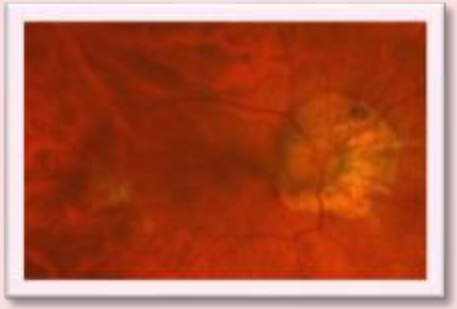
- **OS now: VA 20/80−**, down from 20/30. Persistent **subretinal fluid** and **PED** four weeks after the last 8 mg injection.

- He is adherent, he is maximized across three mechanistic classes, and he is still not dry. Drug failure, barrier failure, or tissue already lost?

ERM = epiretinal membrane; PED = pigment epithelial detachment; PSC = posterior subcapsular cataract; SHRM = subretinal hyperreflective material.

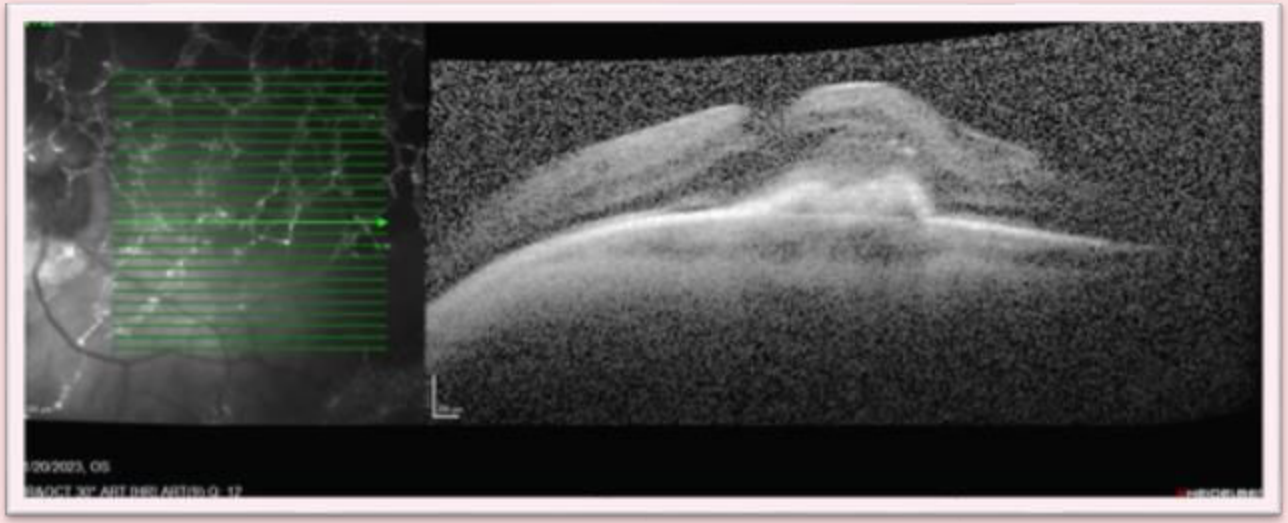
nAMD case · Baseline: PED, subretinal fluid, SHRM (OS)



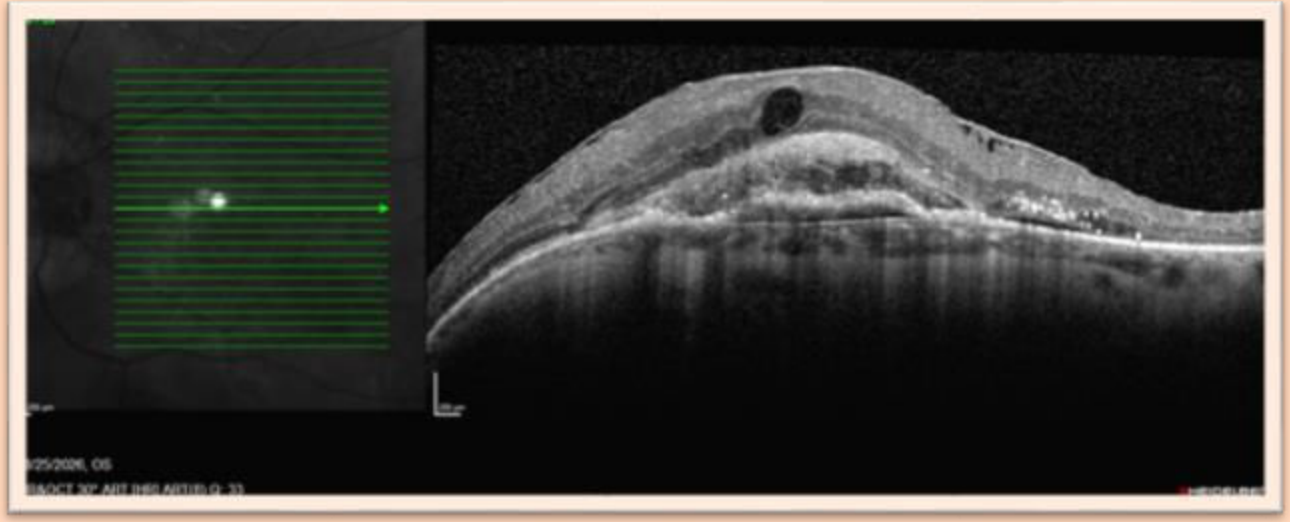




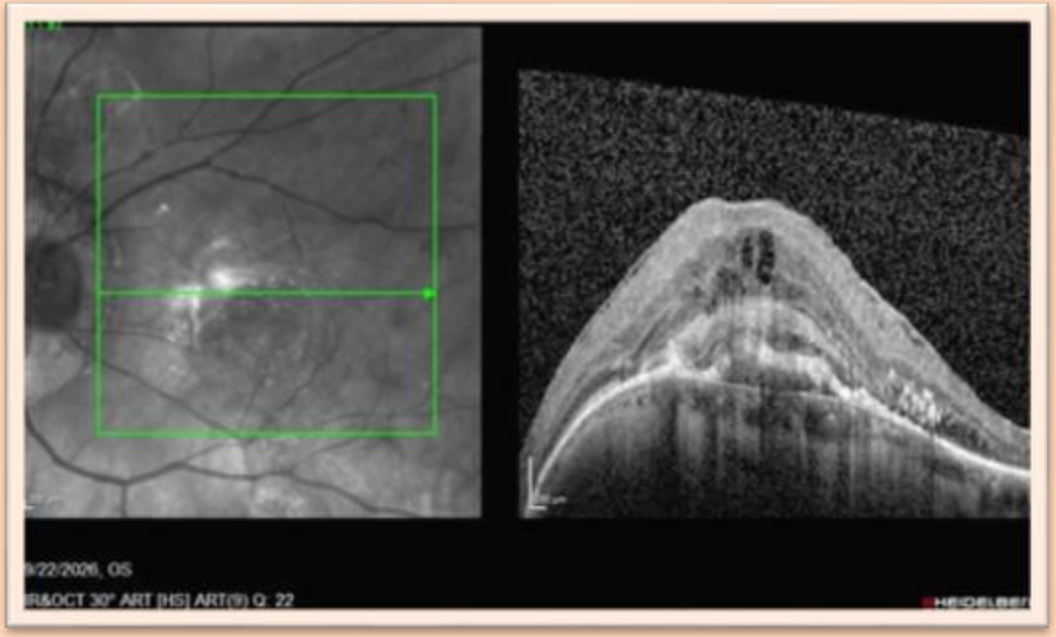
nAMD case · VA 20/30−, after ranibizumab ×7 every 4–5 weeks — faricimab started



nAMD case · VA 20/80−, after faricimab ×15 and aflibercept 8 mg ×18 every 5 weeks



nAMD case · VA 20/80−, 4 weeks after the last aflibercept 8 mg injection



Audience Response



Which finding on Phil's OCT most strongly predicts that vision will not recover, regardless of further anti-VEGF treatment?

A. New or increasing subretinal fluid
B. Persistent intraretinal fluid
C. A growing or refractory pigment epithelial detachment
D. Subretinal hyperreflective material or early fibrosis
E. Outer retinal atrophy or ellipsoid zone loss
F. I’m not sure

CME OUTFITTERS

Optimize, Switch, or Refer

Confirm all four before assigning a category:

1. Loading complete (≥3 injections)
2. Interval maintained
3. Imaging adequate (same device, central 1-mm subfield)
4. Confounders excluded (VMT/ERM traction, atrophy, fibrosis; in nAMD also PCV, CSC).

If the interval was not maintained, score the eye, flag it undertreated, and go to Exit 1.

	EXIT 1: OPTIMIZE	EXIT 2: SWITCH	EXIT 3: REFER
Who	Partial response — or Poor in the primary or secondary window — or any eye flagged undertreated	Poor in the late window, Poor persisting after one optimization cycle, or Non-response	Diagnosis in question, or non-response after a documented class switch
Do	**Hold or shorten the interval.** Complete ≥5 consecutive injections before declaring failure. Check delivery before biology. In DME, address glycemic, BP, and lipid control.	**Change mechanistic class, not just product:** VEGF-A ± PlGF → + Ang-2 → corticosteroid (DME) → sustained delivery. PDT if PCV confirmed on ICGA.	**Multimodal imaging;** ICGA for PED progression; surgical opinion for VMT/ERM; clinical-trial candidacy where an investigational target is being studied.
Re-score	Next decision visit, same three domains	After a full loading course on the new class	
nAMD Patient Case	**Done.** Seven ranibizumab q4–5w, then 33 more injections, interval never extended, adherence complete.	**Done.** Three classes exhausted: VEGF-A, dual Ang-2/VEGF-A, high-dose VEGF trap.	→ **Here.** PED + SHRM: ICGA to exclude PCV. ERM with pseudohole: is traction contributing? Trial candidacy for a barrier-directed target. And the honest alternative — tissue already lost.

CSC = central serous chorioretinopathy; ICGA = indocyanine green angiography; PCV = polypoidal choroidal vasculopathy; PDT = photodynamic therapy; VMT = vitreomacular traction.

Amoaku WM, et al. *Eye (Lond)*. 2015;29(6):721-731. Jhaveri CD, et al. *N Engl J Med*. 2022;387(8):692-703. Lim JI, et al. *Ophthalmology*. 2025;132(4):P75-P162. Vemulakonda GA, et al. *Ophthalmology*. 2025;132(4):P1-P74. Full pathway: CME Outfitters Clinical Points download.

Four Things to Take Home

1 Rule out “not enough drug” first

- Loading complete, interval held, imaging adequate, confounders excluded.
- Delivery gaps look exactly like a biologic plateau on OCT. Check the clock before the biology.

2 Wrong target: the barrier has more than one input

- In eyes that fail anti-VEGF, Ang-2 and inflammatory cytokines can stay high while VEGF falls.
- Dual Ang-2/VEGF-A inhibition is approved; Tie2 and Wnt agonists are in pivotal trials.

3 Too late: define “not responding” early and objectively

- After 3 monthly injections: < 5 ETDRS letters gained or < 10% reduction in central subfield thickness = limited early response.
- Document a decision at that visit — before DRIL and atrophy set the ceiling.

4 Read the new data on its own terms

- BRUNELLO year 1 (Wnt agonist, DME): both doses non-inferior to ranibizumab (+9.1 and +8.7 vs +11.8 letters), but more PDR and AE discontinuations.
- Mechanism is a reason to study, not proof of benefit.

Gonzalez VH, et al. *Am J Ophthalmol*. 2016;172:72-79. Lim JI, et al. *Ophthalmology*. 2025;132(4):P75-P162. Yang F, et al. *Eye Vis (Lond)*. 2026;13(1):12. D’Amico D. American Academy of Ophthalmology (AAO) Annual Meeting. 2026.

QUESTIONS & ANSWERS



Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- Over the next **3 months**, at the first visit after the third loading injection, **record** for every DME or nAMD patient whether vision gain is under 5 letters or central subfield thickness reduction is under 10%, and document the decision made at that visit
- Over the next **3 months**, when a patient asks about a new or emerging treatment, **explain** the mechanism it targets and whether it is approved or investigational
- Over the next **3 months**, for patients with persistent fluid on anti-VEGF therapy, **document the OCT features that bear on visual potential** before the next treatment decision

Additional Resources

Visit www.cmeoutfitters.com for clinical information and certified educational activities



CME OUTFITTERS

Visit the Ophthalmology Hub

Free resources and education to educate health care professionals and patients

https://www.cmeoutfitters.com/practice/ophthalmology-hub/

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In-Person

Livestream

CME for MIPS Improvement Activity

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- Actively participate today by responding to ARS questions and/or asking the faculty questions
- Complete the post-test and activity evaluation at the link provided
- Over the next 3 months, actively work to incorporate improvements from this presentation into your clinical practice
- In approximately 3 months, complete the follow-up survey from CME Outfitters

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CME OUTFITTERS

Beyond VEGF

Understanding Blood-Retinal Barrier Biology and Emerging Mechanisms in DME and Neovascular AMD



This activity is supported through an independent educational grant from Merck & Co., Inc., Rahway, NJ, USA.