POWERED BY bmc

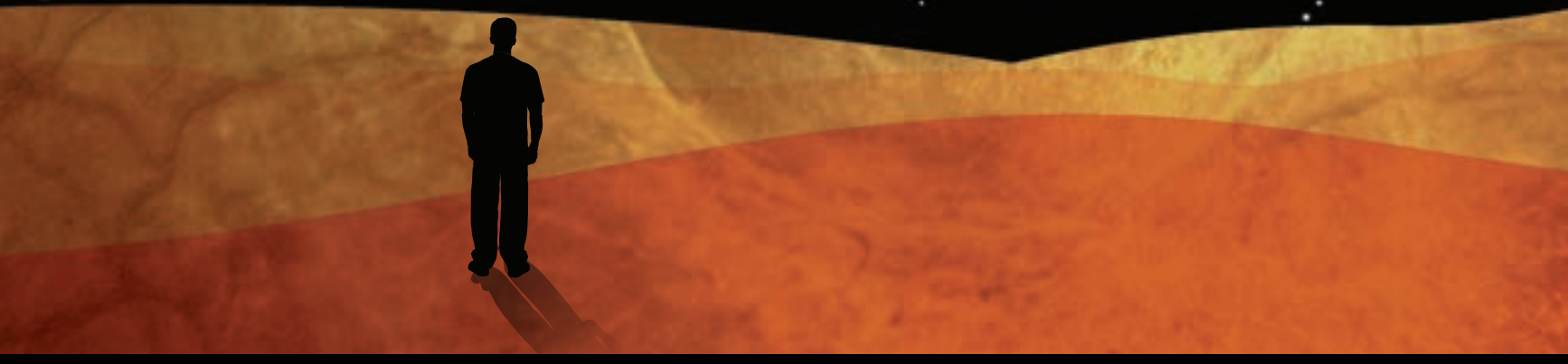
RT
Retina Today

SEPTEMBER 2025 VOL. 20, NO. 6
RETINATODAY.COM

eyetube

# NEW FRONTIERS IN DIABETES CARE

A look at the latest advances reshaping your management approach.



MODERN DIABETES CARE: WHAT YOU NEED TO KNOW

UTILITY OF FLUORESCEIN ANGIOGRAPHY IN DME

TEACHING ADVANCED MEMBRANE DISSECTION

The **first and only** FDA-approved treatment for adults with idiopathic macular telangiectasia type 2 (MacTel)

# ENCELTO™

(revakinagene taroretcel-lwey)

implant, for intravitreal use

## Harness the tech with the survival effect ON PHOTORECEPTORS[1]

**See the data behind ENCELTO**

Scan the QR code or visit ENCELTO.com/ecp

## INDICATIONS AND USAGE

ENCELTO is an allogeneic encapsulated cell-based gene therapy indicated for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

ENCELTO is contraindicated in patients with active or suspected ocular or periocular infections, and in patients with known hypersensitivity to Endothelial Serum Free Media (Endo-SFM).

### WARNINGS AND PRECAUTIONS

ENCELTO implantation surgery and/or implantation related procedures have been associated with the following:

**Severe Vision Loss**

Severe vision loss defined as three or more lines of visual acuity loss [≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters] has occurred following ENCELTO implantation. Monitor patients for signs and symptoms of vision loss and manage as clinically indicated.

**Infectious Endophthalmitis**

Infectious endophthalmitis may occur following ENCELTO implantation. Signs and symptoms of infectious endophthalmitis include progressively worsening eye pain, vision loss, or scleral and conjunctival injection. To mitigate the risk of endophthalmitis, use proper aseptic surgical technique for ENCELTO implantation. Monitor patients for signs or symptoms of infectious endophthalmitis. Remove ENCELTO implant if infectious endophthalmitis occurs and manage symptoms according to clinical practice.

**Retinal Tear and Detachment**

Retinal tears and retinal detachment may occur following ENCELTO implantation. Signs and symptoms of retinal tears include acute onset of flashing lights, floaters, and/or loss of visual acuity. Signs and symptoms of retinal detachment may include progressive visual field loss and/or loss of visual acuity. Use standard vitreoretinal surgical techniques during ENCELTO implantation to minimize the risk of retinal tears and retinal detachment. Monitor for any signs or symptoms of retinal tear and/or retinal detachment. Treat rhegmatogenous retinal detachment and retinal tears promptly. Remove ENCELTO implant, if vitrectomy with a complete gas fill or silicone oil fill is required.

**Vitreous Hemorrhage**

Vitreous hemorrhage, which may result in temporary vision loss, has occurred following ENCELTO implantation. Patients receiving antithrombotic medication (e.g., oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. To reduce the risk of vitreous hemorrhage, interrupt antithrombotic medications prior to the ENCELTO implantation. Vitrectomy surgery may be necessary to clear severe, recurrent, or non-clearing vitreous hemorrhage. If the patient has a late onset vitreous hemorrhage (greater than one year following ENCELTO implantation surgery), examine the ENCELTO implantation site for possible implant extrusion. If implant extrusion has occurred, surgically reposition ENCELTO.

**Implant Extrusion**

Implant extrusion through the initial scleral wound has occurred following ENCELTO implantation. Signs and symptoms of implant extrusion include recurrent uveitis, vitreous hemorrhage, eye pain more than one year after implantation, or visibility of titanium fixation loop under the conjunctiva. To reduce the risk of implant extrusion, carefully follow the specific surgical steps for ENCELTO implantation.

Evaluate patients after 6 months to confirm proper positioning of ENCELTO and then annually. If ENCELTO begins to extrude, surgically reposition ENCELTO to a proper scleral wound depth either in the same site or in the opposing inferior quadrant of the vitreous cavity.

**Cataract Formation**

Cataract formation, including cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities, has occurred following ENCELTO implantation. To reduce the risk of ENCELTO-related cataract formation or progression, carefully follow the specific surgical steps for ENCELTO implantation.

**Suture Related Complications**

Suture related complications, including conjunctival erosions due to suture tips and suture knots, have occurred following ENCELTO implantation.

To mitigate the risk of suture related complications, carefully follow the specific surgical steps for ENCELTO implantation and manage suture-related complications as clinically indicated.

**Delayed Dark Adaptation**

Delayed Dark Adaptation, a delay in the ability to adjust vision from a bright lighting condition to a dim lighting, has occurred following ENCELTO administration which remained unchanged for the duration of study follow up. Advise patients to take caution while driving and navigating in the dark.

### ADVERSE REACTIONS

The most common adverse reactions (≥2%) reported with ENCELTO were conjunctival hemorrhage, delayed dark adaptation, foreign body sensation, eye pain, suture related complications, miosis, conjunctival hyperemia, eye pruritus, ocular discomfort, vitreous hemorrhage, blurred vision, headache, dry eye, eye irritation, cataract progression or formation, vitreous floaters, severe vision loss, eye discharge, anterior chamber cell, iridocyclitis.

**Please see Brief Summary of full Prescribing Information on following pages.**

**Reference:** ENCELTO [prescribing information]. Cumberland, RI. Neurotech Pharmaceuticals, Inc.

neurotech

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**This Brief Summary does not include all of the information needed to use ENCELTO™ safely and effectively.**

**See full Prescribing Information for ENCELTO.**

**ENCELTO (revakinagene taroretcel-lwey) implant, for intravitreal use**

**Initial U.S. Approval: 2025**

## INDICATIONS AND USAGE

ENCELTO is indicated for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

## DOSAGE AND ADMINISTRATION

### Recommended Dose

**For intravitreal implantation only**

- ENCELTO is administered by a single surgical intravitreal procedure performed by a qualified ophthalmologist.
- The recommended dose is one ENCELTO implant per affected eye. Each ENCELTO implant contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing recombinant human ciliary neurotrophic factor (rhCNTF) (NTC-201-6A cell line), a neurotrophic factor.

## CONTRAINDICATIONS

**ENCELTO is contraindicated in patients with:**

- Active or suspected ocular or periocular infections.
- Known hypersensitivity to Endothelial Serum Free Media (Endo-SFM)

## WARNINGS AND PRECAUTIONS

### Severe Vision Loss

Severe vision loss defined as three or more lines of visual acuity loss [≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters] has occurred following ENCELTO implantation. Monitor patients for signs and symptoms of vision loss and manage as clinically indicated.

### Infectious Endophthalmitis

Infectious endophthalmitis may occur following ENCELTO implantation. Signs and symptoms of infectious endophthalmitis include progressively worsening eye pain, vision loss, or scleral and conjunctival injection. To mitigate the risk of endophthalmitis, use proper aseptic surgical technique for ENCELTO implantation. Monitor patients for signs or symptoms of infectious endophthalmitis. Remove ENCELTO implant if infectious endophthalmitis occurs and manage symptoms according to clinical practice.

### Retinal Tear and Detachment

Retinal tears and retinal detachment may occur following ENCELTO implantation. Signs and symptoms of retinal tears include acute onset of flashing lights, floaters, and/or loss of visual acuity. Signs and symptoms of retinal detachment may include progressive visual field loss and/or loss of visual acuity. Use standard vitreoretinal surgical techniques during ENCELTO implantation to minimize the risk of retinal tears and retinal detachment. Monitor for any signs or symptoms of retinal tear and/or retinal detachment. Treat rhegmatogenous retinal detachment and retinal tears promptly. Remove ENCELTO implant, if vitrectomy with a complete gas fill or silicone oil fill is required.

### Vitreous Hemorrhage

Vitreous hemorrhage, which may result in temporary vision loss, has occurred following ENCELTO implantation. Patients receiving antithrombotic medication (e.g., oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. To reduce the risk of vitreous hemorrhage, interrupt antithrombotic medications prior to the ENCELTO implantation. Vitrectomy surgery may be necessary to clear severe, recurrent, or non-clearing vitreous hemorrhage. If the patient has a late onset vitreous hemorrhage (greater than one year following ENCELTO implantation surgery), examine the ENCELTO implantation site for possible implant extrusion. If implant extrusion has occurred, surgically reposition ENCELTO.

### Implant Extrusion

Implant extrusion through the initial scleral wound has occurred following ENCELTO implantation. Signs and symptoms of implant extrusion include recurrent uveitis, vitreous hemorrhage, eye pain more than one year after implantation, or visibility of titanium fixation loop under the conjunctiva. To reduce the risk of implant extrusion, carefully follow the specific surgical steps for ENCELTO implantation.

Evaluate patients after 6 months to confirm proper positioning of ENCELTO and then annually. If ENCELTO begins to extrude, surgically reposition ENCELTO to a proper scleral wound depth either in the same site or in the opposing inferior quadrant of the vitreous cavity.

### Cataract Formation

Cataract formation, including cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities, has occurred following ENCELTO implantation. To reduce the risk of ENCELTO-related cataract formation or progression, carefully follow the specific surgical steps for ENCELTO implantation.

### Suture Related Complications

Suture related complications, including conjunctival erosions due to suture tips and suture knots, have occurred following ENCELTO implantation.

To mitigate the risk of suture related complications, carefully follow the specific surgical steps for ENCELTO implantation and manage suture-related complications as clinically indicated.

### Delayed Dark Adaptation

Delayed Dark Adaptation, a delay in the ability to adjust vision from a bright lighting condition to a dim lighting, has occurred following ENCELTO administration which remained unchanged for the duration of study follow up. Advise patients to take caution while driving and navigating in the dark.

## ADVERSE REACTIONS

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

## ADVERSE REACTIONS (cont'd)

### Clinical Trials Experience (cont'd)

The safety data described in this section reflects exposure to ENCELTO in two clinical trials, Study 1 (NTMT-03-A) and Study 2 (NTMT-03-B) and are pooled for analysis. A total of 117 patients received ENCELTO, and 111 patients underwent a sham procedure and were followed for a duration of 24 months.

Serious adverse reactions occurred in six patients (5%) including suture related complications (n=5) and implant extrusion (n=1).

Table 1 lists the most common adverse reactions that occurred in ≥2% patients and with higher frequency in ENCELTO group compared to Sham group in Study 1 and Study 2.

**Table 1. Adverse Reactions occurring in ≥2% of Patients and with higher frequency in ENCELTO group compared to Sham group in ENCELTO studies***

| Adverse Reactions | ENCELTO (N=117) n (%) | Sham (N=111) n (%) |
|---|---|---|
| Conjunctival hemorrhage | 36 (31) | 29 (26) |
| Delayed dark adaptation | 27 (23.1) | 1 (1) |
| Foreign body sensation in eyes | 18 (15) | 15 (13.5) |
| Eye pain | 18 (15) | 10 (9) |
| Suture related complication** | 18 (15.4) | 3 (2.7) |
| Miosis | 18 (15.4) | 0 (0.0) |
| Conjunctival hyperemia | 13 (11) | 9 (8) |
| Eye pruritus | 10 (9) | 4 (3.6) |
| Ocular discomfort | 10 (9) | 1 (1) |
| Vitreous hemorrhage | 10 (8.5) | 0 (0.0) |
| Vision blurred | 8 (7) | 4 (4) |
| Headache | 8 (7) | 1 (1) |
| Dry eye | 7 (6) | 2 (2) |
| Eye irritation | 6 (5.1) | 2 (2) |
| Cumulative cataract incidence | 6 (5) | 0 (0) |
| Vitreous floaters | 6 (5) | 0 (0.0) |
| Severe visual loss>15 letters*** | 4 (3) | 0 (0) |
| Eye discharge | 4 (3.4) | 1 (0.9) |
| Anterior chamber cell | 4 (3.4) | 0 (0.0) |
| Iridocyclitis | 3 (2.6) | 0 (0) |

*Pooled data from Study 1 and Study 2; Adverse reaction rates were comparable between the two studies

**Suture related complications include exposed suture, foreign body sensation, conjunctival wound dehiscence, painful sutures, suture irritation, suture granuloma, scleral wound opening, and itchy suture

***Includes one case of visual loss due to cataract formation which remained unresolved at the end of the study

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Risk Summary

There are no data on the use of ENCELTO in pregnant women. Endogenous CNTF is naturally found in maternal plasma, placental cells, and umbilical cord blood. It is not known if the use of ENCELTO increases CNTF above naturally occurring levels in these tissues.

In animal reproduction studies, subcutaneous administration of rhCNTF to pregnant rats and rabbits demonstrated no evidence of teratogenic effects on the fetus. However, when administered to rabbits at a dose level of 10ug/kg/day, a decrease in implantations and live fetuses was observed. When administered to rats at a dose level of 100ug/kg/day a decrease in corpora lutea was observed.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

*Animal Data*

See *Risk Summary* for details on data.

### Lactation

Risk Summary

There is no data on the presence of ENCELTO in human milk, its effects on the breastfed infant, or its impact on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENCELTO and any potential adverse effects on the breastfed infant from rhCNTF or from the underlying maternal condition.

### Pediatric Use

The safety and effectiveness of ENCELTO have not been established in pediatric patients.

### Geriatric Use

There were 38 patients (32%) 65 years of age and older and two patients (1%) 75 years of age and older in Study 1 and Study 2 who received ENCELTO. Clinical studies of ENCELTO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

Manufactured for:
Neurotech Pharmaceuticals, Inc.
Cumberland, RI 02864

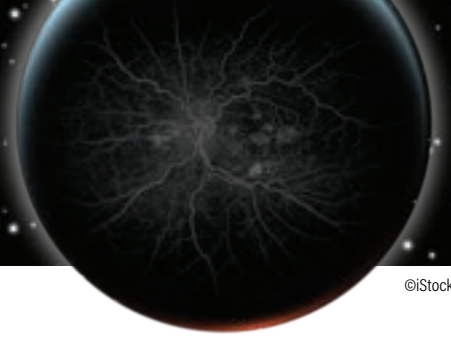


ENCELTO™ (revakinagene taroretcel-lwey) implant, for intravitreal use | neurotech


US-EO-PM-250200024 04/2025

*Retina Today (ISSN 1942-1257) © 2025 Bryn Mawr Communications LLC is published January/February, March, April, May/June, July/August, September, October, and November/December by Bryn Mawr Communications LLC, 125 East Elm Street, Suite 400, Conshohocken, PA 19428. Subscription is free to all applicable US retina physicians. All others, applicable subscription charges apply. For subscription information call +1 800 492 1267 (US only) or e-mail retinatoday@bmctoday.com. Pending periodical postage paid at Wayne PA and additional entry offices. POSTMASTER Please send address changes to Bryn Mawr Communications LLC, 125 East Elm Street, Suite 400, Conshohocken, PA 19428. Bryn Mawr Communications LLC provides certain customer contact data, which may include customer names, addresses, phone numbers and e-mail addresses, to third parties for promotional and/or marketing purposes. If you do not wish Bryn Mawr Communications LLC to make your contact information available to third parties for any marketing purposes, please contact us at 800-492-1267 or e-mail us at retinatoday@bmctoday.com. This publication is intended for health care professionals and providers only. The information contained in this publication, including text, graphics and images, is for informational purposes only and is not intended to be a substitute for professional medical advice. Bryn Mawr Communications LLC, via its Editors and the Publisher, accepts no responsibility for any injury or damage to persons or property occasioned through the implementation of any ideas or use of any product described herein. While great care is taken by the Publisher and Editors to ensure that all information is accurate, it is recommended that readers seek independent verification of advice on drug or other product usage, surgical techniques and clinical processes prior to their use. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors, the publication or the Editorial Board. References made in articles may indicate uses of medical equipment or drugs at dosages, for periods of time and in combinations not included in the current prescribing information. Inclusion of advertising material in this publication, or in supplements thereof, does not constitute any representation or guarantee by Bryn Mawr Communications LLC of the quality of such products or of the claims made by the manufacturers.*

# TABLE OF CONTENTS



©iStockphoto.com

## FEATURED ARTICLES



### ONLINE FEATURE



## DEPARTMENTS



### ONLINE EXCLUSIVE

VALEDA®

Light Delivery System

# The First and Only FDA-Authorized Treatment for Dry AMD that Improves Vision

## It's Time for Patients to See Their Future


MyValeda.com

LumiThera®

Rx Only

Refer to the Valeda User Manual for indications for use and important safety information.

# A CALL FOR HOLISTIC CARE


In the midst of the fall conference schedule, many of us have been jet-setting, hob-knobbing, and slide deck-checking all over the United States and abroad. A number of hot topics have been buzzing around the conference halls, including the loss of Good Days funding,[1] the integration of new dry AMD therapies (such as complement inhibitors for geographic atrophy and LumiThera's Valeda Light Delivery System for intermediate dry AMD) into the clinic, the launch of Alcon's Unity vitreoretinal cataract system, and the novel implant to treat macular telangiectasia type 2, revakinagene taroretcel-lwey (Encelto, Neurotech).

One topic of particular interest, especially for this issue, has been the massive shift in diabetes care, including new systemic drugs, advanced disease management tools, and novel treatments for diabetic retinopathy (DR) and diabetic macular edema (DME). We were happy to see several lectures focused on systemic care at the annual American Society of Retina Specialists meeting in Long Beach, California. For example, Amer Alsoudi, MD, an ophthalmology resident at Baylor, shared his team's data showing a reduced risk of vision-threatening complications for patients with nonproliferative DR who used a continuous glucose monitor for 1 year compared with those who did not use the device.[2]

Stemming from these talks, a few colleagues anecdotally noted that while diabetes is on the rise, the risk of vision-threatening complications isn't necessarily keeping pace. And they were right. A new study in *Ophthalmology* found that, although the prevalence of diabetic retinal disease increased steadily between 2001 and 2021, vision-threatening complications rose until 2016 but have since decreased each year through 2021 (Table).[3]

While the decrease in the rate of complications is small (the incidence of vision-threatening complications was 7.5% in 2016 and 6.9% in 2021),[3] it's statistically significant and, more importantly, a sign of improvement in our field. Retina specialists are getting better at screening patients, diagnosing early, and treating properly. On top of that, today's systemic care now includes continuous glucose monitors, digital diabetes management platforms, and next-generation therapies such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

Our patients with diabetes are some of our most complicated patients to care for, and they are requiring more chair time, closer monitoring, and more patient education. Because we can always do better—and we *must* do better—this issue is designed to help you understand the holistic treatment landscape for diabetes.

Ehsan Rahimy, MD, and his team at Byers Eye Institute discuss the effect of new systemic care options on the eye, while Aleksandra V. Rachitskaya, MD, and her team at Cole Eye dive deeper into GLP-1 RAs.

In addition, Jorge C. P. Rocha, MD, PhD, and Majda Hadziahmetovic, MD, touch on the use of AI to boost our screening programs. For more on diabetic eye disease screening, head online to retinatoday.com to read about a large-scale screening initiative, Diabetes Day, that first launched at Wills Eye Hospital in 2022. This year's program ran statewide in Pennsylvania, and the organizers hope Diabetes Day continues to grow and help more patients connect with specialty care.

We also have articles on imaging DME with fluorescein angiography and OCT angiography, managing patients with DR and good vision, and a very detailed article on teaching (not just performing) fibrovascular membrane dissection.

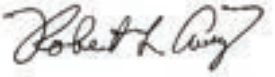
So, if you see a patient this week struggling to maintain control of their hemoglobin A1c (we all have them in our clinics), maybe now is the time to suggest a new medication or mention the value of a digital monitoring platform—these systemic changes might be the difference between long-term visual health and blinding disease. ■

**TABLE. PREVALENCE OF DIABETIC EYE DISEASE AND VISION-THREATENING COMPLICATIONS, 2001-2021.[3]**

| | 2001 | 2007 | 2016 | 2021 |
|---|---|---|---|---|
| Diabetic Retinal Disease | 13.6% | 10.9% | 14.5%* | 20.8% |
| Vision-Threatening Complications | 5.7%* | 5.2% | 7.5% | 6.9% |
| Diabetic Macular Edema | 2.8% | 3.2% | 5.4% | 4.9% |

*Estimate based on chart published in VanderBeek BL et al.[3]

1. Lai M. The impact of Good Days' underfunding on retinal disease management: Insights from a national survey of American Society of Retina Specialists members. Presented at ASRS. August 2, 2025; Long Beach, California.
2. Alsoudi A, Wai KM, Koo E, Koo, E, Mruthyunjaya P, Rahimy E. Reduced rates of diabetic retinopathy complications with use of continuous glucose monitoring. *Nature Sci Rep*. 2025;15:25215.
3. VanderBeek BL, Yu Y, Cardillo S, Hubbard R. Twenty-Year Trends in Prevalence and Incidence of Diabetic Retinal Disease. *Ophthalmology*. 2025;132(7):767-774.

**ALLEN C. HO, MD**
**CHIEF MEDICAL EDITOR**

**ROBERT L. AVERY, MD**
**ASSOCIATE MEDICAL EDITOR**

RT NEWS

SEPTEMBER 2025

VOL. 20, NO. 6 | RETINATODAY.COM

# ANTI-CANCER DRUG MAY REDUCE RISK OF PVR

New data suggest that the use of systemic mammalian target of rapamycin inhibitor (MTI) therapy, a common cancer treatment, may help prevent the development of proliferative vitreoretinopathy (PVR).[1,2] A recent study found that patients who underwent initial retinal detachment (RD) repair while being treated with systemic MTI therapy were less likely to develop a subsequent PVR-related RD.[1]

This retrospective cohort study from 15 countries included 681 patients who underwent primary RD repair while receiving systemic MTI therapy at least 3 months before and 1 year after the initial RD repair. The study cohort was compared with a control group of 47,626 patients.[1]

At 1 year, concurrent use of systemic MTI therapy was associated with a decreased risk of developing a PVR-related RD (relative risk: .58, $P = .03$) compared with matched patients who underwent initial RD repair without exposure to systemic MTI therapy. Moreover, use of systemic MTI therapy was associated with a decreased risk of requiring subsequent vitrectomy (relative risk: .57, $P < .001$) and complex RD repair (relative risk: .60, $P = .01$) compared with matched patients who underwent initial RD repair without exposure to MTI therapy at 1 year.[1]

1. Panwar V, Singh A, Bhatt M, et al. Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. *Signal Transduct Target Ther.* 2023 Oct 2;8(1):375.
2. Alsoudi AF, Loya A, Wai K, et al. Mammalian target rapamycin inhibition as a therapeutic target for prevention of proliferative [published online ahead of print August 7, 2025]. *JAMA Ophthalmol.*

## WIDEFIELD ICGA AND OCTA PROVE RELIABLE IN EVALUATING CSC

A team of researchers recently found that widefield OCT angiography (OCTA) was comparable with widefield ICG angiography (ICGA) when assessing choroidal vein distribution patterns in eyes with central serous chorioretinopathy (CSC). The data establish widefield OCTA as a reliable alternative for evaluating CSC choroidal vasculature.[1]

This retrospective analysis included 105 patients and a total of 151 eyes with CSC. In eyes with CSC, widefield ICGA and widefield OCTA detected similar rates of asymmetric distribution (76.82% vs 78.14%, $P = .783$), and there were no significant differences in the number and location of dominant vortex veins ($P > .05$). Both imaging devices recognized the highest proportion of cases with one dominant vortex vein, followed by cases with two dominant veins and those with symmetric venous distribution.[1]

1. Hao X, Pu J, Li M, et al. Evaluation of choroidal vein distribution pattern and choroidal vessel parameters in patients with central serous chorioretinopathy using widefield ICGA and widefield OCTA [published online ahead of print August 1, 2025]. *Am J Ophthalmol.*

## Eyewire+ Pharma Update

- **Alcon** entered an agreement to acquire Staar Surgical, which includes the EVO family of implantable collamer lens products.
- **Annexon** completed enrollment of its phase 3 ARCHER II trial evaluating ANX007 (vonaprument) for the treatment of dry AMD.
- **EyePoint Pharmaceuticals** completed enrollment for the phase 3 LUCIA trial, evaluating the vorolanib intravitreal insert (EYP1901/ Duravyu) for the treatment of wet AMD.
- **Harrow** announced an agreement with Samsung Bioepis to secure exclusive rights to commercialize the latter's biosimilar portfolio.
- **Neurotech Pharmaceuticals** announced the first commercial surgery for revakinagene taroretcel-lwey (Encelto) for Mac-Tel type 2.

Want more retina news from *Eyewire+*?

## ADVOCATES MOBILIZE IN SUPPORT OF NEI

Eye care organizations are rallying to fight against proposals to cut federal vision funding and fold the National Eye Institute (NEI) into a broader institute on brain and dental research. Restructuring the NEI would dilute its mission, compromise research continuity, and endanger progress in treating blinding diseases, according to the coalition of eye care organizations.[1] The group unveiled a nationwide educational and advocacy initiative, #SeeWhatMatters, that aims to highlight the NEI's integral role in eye care research. The campaign will use seewhatmatters.org to empower stakeholders to make their voices heard in Congress.[1] ■

1. Vision advocates rally to defend national eye institute from funding cuts and consolidation threats. Eyewire+. August 1, 2025. Accessed August 11, 2025. eyewire.news/news/vision-advocates-rally-to-defend-national-eye-institute-from-funding-cuts-and-consolidation-threats

# TOP PANEL DISCUSSIONS AT ARDS 2025

Experts share medical and surgical tips and explore the effects of shifting practice patterns.

BY JONATHAN N. LEVENSON, MD

*The 53rd annual Aspen Retinal Detachment Society (ARDS) meeting, held March 1 – 5, 2025, in Snowmass Village, Colorado, included several excellent panel discussions. These are always my favorite part of the meeting because the panelists share their varied approaches to surgical and medical retina, the audience engages with the conversation, and we all learn so much. I hope you enjoy the recap below, and I look forward to seeing you at next year's meeting, scheduled for February 28 – March 4, 2026!*

**– Timothy G. Murray, MD, MBA**

As part of the 53rd annual ARDS meeting, experts gathered for three lively panel discussions that touched on everything from complex diabetic eye surgery and macular hole repair to diagnostic imaging, wet AMD therapies, and shifting practice patterns. Here, I summarize the key takeaways.

## PANEL 1: RETINAL DETACHMENTS AND MACULAR HOLES

The first panel was moderated by Donald J. D'Amico, MD, and included Audina M. Berrocal, MD; Mrinali P. Gupta, MD; John W. Kitchens, MD; Mario R. Romano, MD, PhD; and Lejla Vajzovic, MD (Figure 1).

The panel opened with a candid discussion of diabetic tractional retinal detachments (RDs). Across the board, panelists reported a shift toward earlier surgical intervention, favoring prompt vitrectomy in cases of persistent vitreous hemorrhage rather than prolonged observation, especially in the absence of a posterior vitreous detachment. Dr. Kitchens noted that early vitrectomy—often within 2 to 3 weeks—can reduce patient burden and potentially improve outcomes, especially with modern instrumentation and techniques.

The experts then debated the role of internal limiting membrane (ILM) peeling in diabetic tractional RD cases. While some advocated for peeling to relieve traction, Dr. Romano warned that in eyes with diabetic Müller cell pathology, ILM manipulation could induce retinal trauma and limit functional recovery. All agreed that careful case selection is critical.

In the setting of diabetic macular edema (DME), steroids were highlighted as the go-to strategy when anti-VEGF agents fail, although functional gains remain a challenge.

Image courtesy of Kevin Caldwell Photography

**Figure 1. The "Let's Talk Surgical Retina" panel included (left to right): Drs. Gupta, Romano, Berrocal, Kitchens, Vajzovic, and D'Amico.**

En face OCT was noted to be a useful tool to better characterize the edema as exudative or structural and to rule out subtle traction. Surgical intervention in diffuse, non-tractional DME was generally not favored.

Macular hole surgery was another major focus of the discussion. For mid-size holes of approximately 400 µm, most panelists still favor standard ILM peeling rather than ILM flap techniques, citing consistently high closure rates. For larger holes or those in myopic eyes, ILM flaps, amniotic membrane grafts, and autologous retinal transplants were discussed; some panelists favored procedural simplicity, while others preferred techniques showing better integration on OCT. Swept-source OCT was highlighted for its utility in postoperative imaging through gas.

4DMT

# At the **4FRONT** of wet AMD

4D Molecular Therapeutics (4DMT) is a late-stage biotechnology company focused on unlocking the full potential of genetic medicines. We're advancing durable and disease-targeted therapeutics to transform treatment paradigms.

Our lead retina program, **4D-150**, is a potential backbone therapy designed to provide multi-year sustained delivery of anti-VEGF (aflibercept and anti-VEGF-C) targeted to the retina with a single intravitreal injection. **4D-150** utilizes our retinotropic intravitreal vector, **R100**, which is designed for routine low dose intravitreal delivery to all layers and regions of the retina.

**4D-150** is currently being studied in the global **4FRONT** Phase 3 program for the treatment of wet age-related macular degeneration.

**Learn more at www.4DMT.com**

Looking ahead, the panelists shared visions for future innovation, including bioengineered scaffolds, platelet-rich plasma-loaded hydrogels, and tools to simplify macular buckling. Next-generation tamponades in particular were thought to be potentially transformative for surgical outcomes and patient quality of life.

## PANEL 2: IMAGING AND WET AMD THERAPY

The next panel, focused on medical retina, was moderated by Timothy G. Murray, MD, MBA, and included Szilard Kiss, MD; John T. Thompson, MD; Carl D. Regillo, MD; and John B. Miller, MD (Figure 2).

This panel explored a variety of diagnostic imaging techniques for wet AMD. Dr. Thompson routinely uses fluorescein angiography (FA) at initial diagnosis, emphasizing its utility for documentation and treatment planning. Others, including Drs. Kiss and Miller, reported rarely using FA and instead favoring OCT and, selectively, OCT angiography (OCTA) in certain ambiguous cases.

While OCTA was praised for its noninvasive depth resolution, limitations in segmentation and interpretability led to differing practice patterns. Some noted that OCTA was particularly useful in pediatric cases and non-AMD conditions, such as retinal vascular anomalies and familial exudative vitreoretinopathy.

Bilateral same-day intravitreal injections for wet AMD were also discussed in depth. Most panelists endorsed this practice, citing evidence that the risk of bilateral endophthalmitis is low when separate vials and lot numbers are used. However, concerns were raised about the legal defensibility of same-lot bilateral injections, especially with compounded agents such as bevacizumab (Avastin, Genentech/Roche).

Drug selection strategies also varied. While some preferred to start all patients on second-generation agents such as 8 mg aflibercept (Eylea HD, Regeneron) or faricimab (Vabysmo, Genentech/Roche), others advocated for initial use of bevacizumab. Recent shortages and reimbursement shifts have made branded drugs more accessible in some practices, while others face increasing challenges due to rising costs and limited patient assistance programs. The panel noted that these pressures are influencing not only drug selection but also injection intervals and use of samples.

## PANEL 3: SHIFTING LANDSCAPES AND PRACTICE PATTERNS

The final panel was moderated by Dr. D'Amico and included Drs. Berrocal, Gupta, Miller, Murray, and Vajzovic. This lively discussion centered on growing concerns about declining access to ORs for emergent retinal cases such as macula-on RDs, endophthalmitis, and intraocular foreign bodies. Community hospitals are increasingly limiting OR time for retinal surgery, leading to some smaller community practices being shut out altogether. Panelists in academic settings noted that this has prompted a surge of emergent cases at their academic centers that have overwhelmed their OR schedules and created anesthesia bottlenecks.

Image courtesy of Kevin Caldwell Photography

**Figure 2. During the "Let's Talk Medical Retina" panel, (left to right) Drs. Thompson, Regillo, Murray, Miller, and Kiss shared their thoughts on diagnostic imaging and wet AMD therapy.**

The panelists identified declining reimbursement for complex retina surgical codes as a root cause. They explained that hospitals lose money on RD repairs and have little incentive to accommodate these cases. Some panelists suggested that office-based surgery could be a viable solution; however, logistical, regulatory, and safety concerns remain barriers to widespread adoption. Many agreed that pneumatic retinopexy may increase in prevalence to help bridge the gap until the OR is available for urgent RD repair.

The panelists agreed that these constraints may affect care delivery models, possibly encouraging the development of concierge practices and incorporating mid-level providers to increase practice efficiency. It may also affect the quality and quantity of fellowship training opportunities for the next generation of retina specialists.

There was broad consensus that organized advocacy and systemic changes are needed to address these issues. A call was made for retina societies to collect data on OR access limitations and advocate for improved reimbursement and policy change to preserve patient access to timely care.

## UNTIL NEXT YEAR...

The 2025 ARDS panels showcased both the clinical advances shaping retina care today and the economic and logistical realities redefining its future. Such robust discussions allow everyone an opportunity to learn from experts in the field and help improve care across the board. Next year's meeting, set for February 28 – March 4, 2026, is sure to deliver another set of top-notch panels to explore advances in the field and barriers to care. ■

**JONATHAN N. LEVENSON, MD**
- Vitreoretinal Surgery Fellow, Weill Cornell Medical College, Department of Ophthalmology, New York, New York
- jnl4002@med.cornell.edu
- Financial disclosure: None

# PNEUMATICS: A FELLOW'S PERSPECTIVE

Keep these tips and tricks in mind as you master pneumatic retinopexy.

BY FLAVIUS BECA, MD

Pneumatic retinopexy is an excellent addition to the retina surgeon's armamentarium. It's very rewarding to take a patient with hand motion vision back to 20/20 in less than 2 weeks, all while avoiding the OR. However, becoming adept at pneumatic retinopexy requires practice. Incorporating a new technique early in solo practice can be daunting, making effective skill acquisition during training even more important. Here, I present some pearls in pneumatic retinopexy management and surgeon development.

## PEARL NO. 1: PRACTICE MAKES PERFECT

Beyond all other tips and tricks, becoming better at pneumatic retinopexy requires practice. As with any procedure, particularly one with as many possible variations as pneumatics, the art is in understanding the nuances. And that can only happen with experience and the confidence gained through repeat success.

You must accept that failure will occur, as is the case with any other skill acquired during fellowship or residency. The fear of failure can be debilitating; however, it is important to realize that a failed pneumatic does not necessarily entail a worse final outcome. In fact, the opposite is often true. A macula-off retinal detachment (RD) can be transformed into a macula-on RD by the time you are in the OR for a vitrectomy. A macula-off detachment can have an attached fovea within hours of bubble injection.

## PEARL NO. 2: START EASY

Depending on who you ask, indications for pneumatic retinopexy can range from restrictive to liberal. Gaining confidence early, however, is more easily done when the ideal candidate is in your chair. Patients with quadratic RDs with single superior tears who are phakic and have no additional peripheral pathology and a clear posterior vitreous detachment make for a much easier initial learning curve.

After five to 10 successful cases, you will feel more comfortable with the mechanics and the pace of pneumatic retinopexy. By this point, you'll likely have mastered the large-volume paracentesis and gas bubble injection without excessive fish eggs and be accustomed to the pace of bubble expansion and the timing of staged laser retinopexy, helping you feel more confident in proceeding with more complex cases.

This is also the time to experiment with staged laser versus cryotherapy at the time of the pneumatic retinopexy. Both approaches have pros and cons, so weighing both is important. While cryotherapy has the benefit of potentially being a one-and-done treatment, patients will have significant chemosis and postoperative discomfort. Laser, on the other hand, can be more difficult through a gas bubble, particularly on a blonde fundus. Bullous RDs can mask the true location of a break, particularly one that is not marked at the time of the pneumatic retinopexy.[1]

## PEARL NO. 3: PATIENT SELECTION AND EXPECTATIONS

Patient selection is critical. In the OR, patients are sedated, and you are in control. In the clinic, the patient is awake, and participation is critical. During the initial examination, consider how the patient tolerates the depressed examination. Let them know that the pneumatic will involve significantly more manipulation in the chair both on the initial day and during follow-up. Make sure

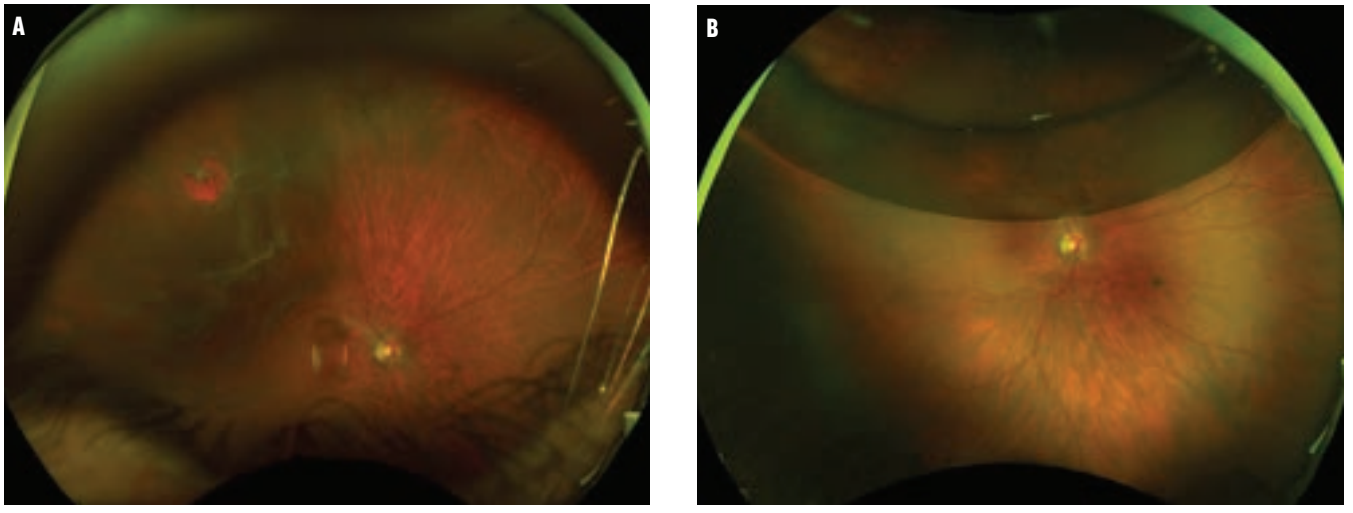



Figure 1. This macula-off RD had breaks at the 9, 10, and 12 clock hours (A). Pneumatic retinopexy with a large bubble allowed for complete staged laser on postoperative day 2 following gas injection (B). At the postoperative month 4 visit, the patient's VA was 20/25, and the retina remained attached.

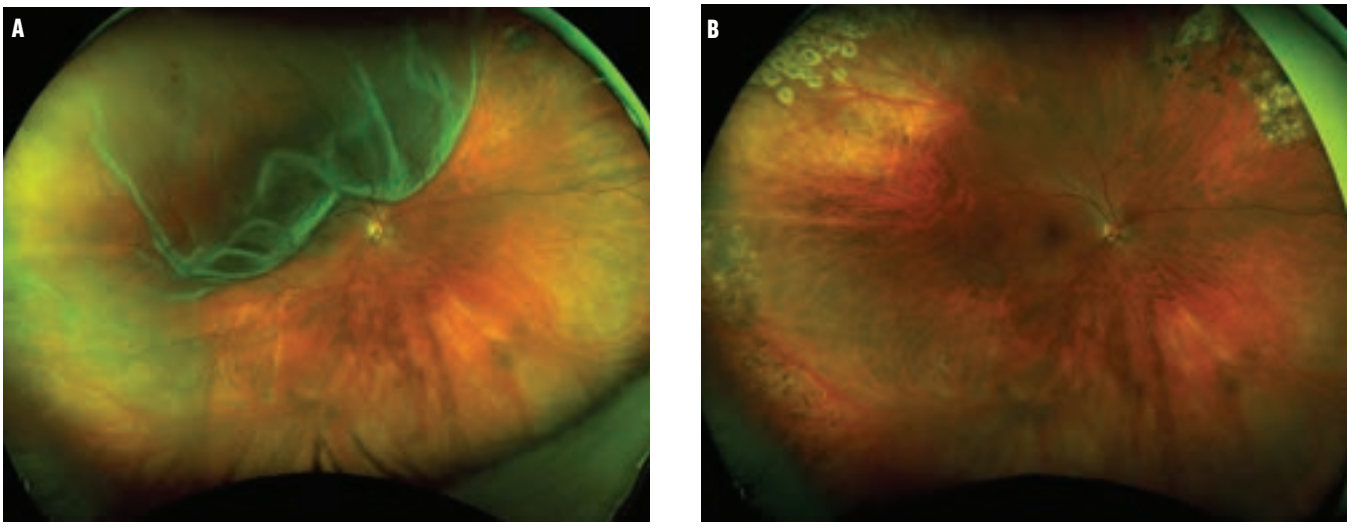



Figure 2. A patient presented with a pseudophakic macula-off rhegmatogenous RD with an operculated retinal hole and inferior lattice (A). The patient's retina remained attached 6 months after pneumatic retinopexy (B).

they know that the procedure may have a lower rate of primary success, require more manipulation in the clinic, and, in the event of failure, result in the same surgery that is initially being deferred.[2,3]

It is useful to know what kind of support, if any, patients have at home and how much of a burden additional clinic visits might be for them.[4] A patient with little support and a long commute is at higher risk for loss to follow-up than the highly motivated patient who has a care provider who is committed to taking them to their frequent visits and enforcing positioning. While we do not have a regimented visit schedule, we see most patients the first day following pneumatic retinopexy. At this visit, we check IOP and can typically apply laser, as even the most bullous of detachments are flat with the use of a large bubble. Patients are then typically extended to weekly visits until the gas resolves (one to three more visits) and then to monthly visits in a pattern similar to surgical patients.

Clinically, consider peripheral pathology, such as atrophic holes, lattice, or even abnormal pigmentary changes. Frequently, a pneumatic will fail not because of inadequate treatment of the original break, but because a new break develops or is initially missed. Meticulous laser of retinal holes and lattice degeneration at the original visit, as well as during the follow-up period once the bullous fluid has resolved, is critical to long-term success.

## PEARL NO. 4: LARGE BUBBLE

One of the most effective tricks that will significantly increase your success rate is using a large gas bubble. The large bubble allows for more effective examination during follow-up, makes staged laser significantly easier, more

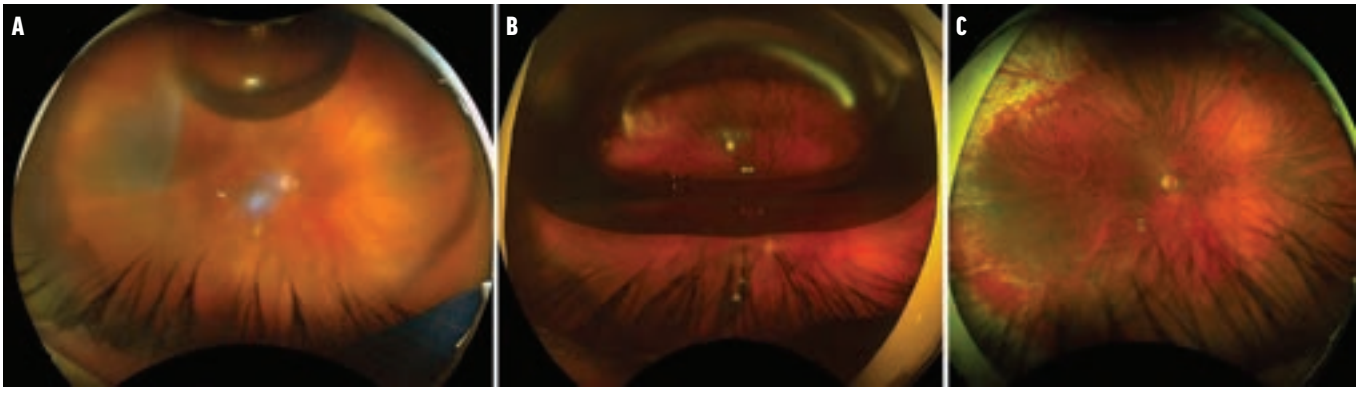



Figure 3. A patient presented with a history of RD and a current macula-off detachment (A). He underwent cryotherapy and pneumatic retinopexy, but a relatively small bubble was used, and he developed new subretinal fluid during follow-up (B). A second bubble was placed, and additional broad peripheral laser was applied. His retina remained attached at the postoperative month 5 visit (C).

**MINOR SETBACKS DO NOT HAVE TO SPELL FAILURE. OCCASIONALLY, A NEW TEAR DEVELOPS, LESS GAS IS INTRODUCED THAN EXPECTED, OR THE PATIENT METABOLIZES THE GAS FASTER THAN EXPECTED. FIND THE SOLUTION.**

quickly displaces submacular fluid, and makes positioning much easier for the patient (Figure 1).

To achieve a large bubble, you must become comfortable with a large-volume anterior chamber paracentesis. In our clinic, we perform the procedure with a speculum while the patient lies on their back in the chair and looks up at the ceiling. With practice, you can use a cotton tip applicator—with 0.4 cc to 0.5 cc taps—to attain persistent pressure near the limbus, even in the phakic patient. This allows you to confidently inject 0.6 cc of gas without having to worry about next-day IOP spikes.

For added security, you can consider prescribing prophylactic dorzolamide/timolol alongside a steroid/antibiotic combination as part of the standard postoperative drop regimen, which can be tapered off during 1 to 2 weeks of follow-up.

## PEARL NO. 5: COMMIT TO THE CAUSE

With the fundamentals in place, progressively more complex cases can quickly become successful cases.

The rare case in which the break cannot be identified, but a superior location is suspected, can be positioned accordingly. Apply laser to the superior clock hours where the break is expected (we prefer laser in cases where broad areas require treatment).[5]

In pseudophakic cases where you might expect to find multiple small far peripheral breaks, close inspection on depressed examination with treatment of areas of peripheral vitreous traction can lead to similar success rates as the clear phakic patient (Figure 2).

Minor setbacks do not have to spell failure. Occasionally, a new tear develops, less gas is introduced than expected, or the patient metabolizes the gas faster than expected. Find the solution. Rather than defaulting to the OR, consider careful re-assessment of the current RD. Rebubbling with positioning to the causative break can turn an apparent failure into a success (Figure 3). ■

1. Muni RH, Kertes PJ. Marking of retinal breaks in detached retina with laser photocoagulation before pneumatic retinopexy: a prospective case series. *Retina*. 2009;29(3):405-408.
2. Hillier RJ, Felfeli T, Berger AR, et al. The pneumatic retinopexy versus vitrectomy for the management of primary rhegmatogenous retinal detachment outcomes randomized trial (PIVOT). *Ophthalmology*. 2019;126(4):531-539.
3. Stewart S, Chan W. Pneumatic retinopexy: patient selection and specific factors. *Clin Ophthalmol*. 2018;12:493-502.
4. Al-Falah M, Muni RH, Kertes PJ. Pneumatic retinopexy: common myths dispelled. *Retina Today*. 2023;18(1):22-24.
5. Lincoff H, Gieser R. Finding the retinal hole. *Arch Ophthalmol*. 1971;85(5):565-569.

**FLAVIUS BECA, MD**
■ Vitreoretinal Surgical Fellow, Mid Atlantic Retina, Wills Eye Hospital, and Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
■ flaviusbeca@gmail.com
■ Financial disclosure: None

# ONE TO WATCH

RT Retina Today

Editorially independent supported by
abbvie
REGENXBIO

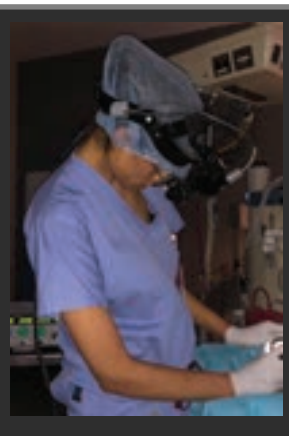
Priya Vakharia, MD, FASRS

## WHERE IT ALL BEGAN

I grew up in Clovis, New Mexico, a small town in the middle of nowhere. My parents were both family medicine doctors, and I witnessed firsthand the joy that they experienced taking care of their patients. I was never pushed to go into medicine but gravitated toward it anyway.

## MY PATH TO RETINA

I went to the Pennsylvania State University/Jefferson combined BS/MD program. I had every intention of going into internal medicine (specifically oncology) because I wanted to work with the most vulnerable patients and help make a difference. However, during my ophthalmology rotation at Wills Eye Hospital, I shadowed in the retina clinic with the current fellow, Rajiv E. Shah, MD. His love of the retina was infectious, and I fell in love with it, too—I loved the pathology, complexity, and ability to help patients in such a meaningful way. I remember shadowing surgery and seeing how scared but grateful the patients were, and I knew I wanted to have that kind of effect. I was so sure of my decision that on my application for ophthalmology residency, I wrote that I wanted to do surgical retina.



**Dr. Vakharia's advice: Be true to yourself, and pursue the avenues that bring you happiness, whether that's clinical trials, working with industry, or being a great community retina specialist. Also, always treat patients the way you would want to be treated—if you follow that rule, you will always do what is best for your patient.**

## SUPPORT ALONG THE WAY

Retina is an incredible group of like-minded people who work hard for our specialty and our patients. I want to call out two of my biggest mentors, Jeffrey S. Heier, MD, and David A. Eichenbaum, MD. Both have been instrumental in shaping my career, providing guidance, and connecting me with opportunities that I would otherwise never have received.

Dr. Heier was an attending during my fellowship, and he shaped how I approach clinic, staff, surgery, and patients. His calm demeanor, compassion, and incredible skill serve as an inspiration to me.

Dr. Eichenbaum has helped shape me as an early-career retina specialist, and he is always available for advice on patient care, my career, or clinical trials. He never stops working, and his leadership and work ethic are inspirational.

I am also incredibly grateful to everyone in my practice at Retina Vitreous Associates of Florida. We have a group of eight doctors who are my best friends and biggest confidantes.

## AN EXPERIENCE TO REMEMBER

I cared for a middle-aged man who had a macula-on retinal detachment in his right eye and a macula-off retinal detachment in his left eye. His surgeries were successful, and he regained a VA of 20/20 OD and 20/30 OS. When I saw him 1 year later, he was so thankful, stating that he saw me on the worst day of his life and is so grateful for the care he received. He said to me, "You will never understand the impact you have had on my life." These words resonated with me, and I was reminded of how great of an effect we can make on our patients. ■

**Priya Vakharia, MD, FASRS,** is a partner at Retina Vitreous Associates of Florida and a collaborative assistant professor at the University of South Florida/Morsani College of Medicine. She holds equity in McKesson and is a consultant or speaker for Abbvie, Adverum, Aliph, ANI, Annexon, Apellis, Astellas, Bausch + Lomb, Bayer, Coherus, Eyepoint, Genentech/Roche, Heidelberg, Notal Vision, Novartis, Ocular Therapeutix, Ocuphire, and Regeneron. She can be reached at **priyasharma141@gmail.com.**

# USING AI TO IDENTIFY PATHOLOGIC MYOPIA AND MYOPIC MACULOPATHY

How research on the use of AI can translate to future clinical applications.

BY YINING WANG, MD; TIEN YIN WONG, MBBS, MMED (OPHTH), MPH, PHD; AND KYOKO OHNO-MATSUI, MD, PHD

Pathologic myopia (PM) is a leading cause of irreversible blindness in East Asia and a growing global public health concern.[1-6] According to the International Myopia Institute, PM is characterized by excessive axial elongation associated with myopia, resulting in structural changes in the posterior segment of the eye, such as posterior staphyloma, myopic maculopathy (MM), and high myopia-associated optic neuropathy.[7]

To standardize the diagnosis of MM, a classification system known as the META-analysis for pathologic myopia (META-PM) was introduced in 2015 based on fundus photographs.[8] This system categorizes MM into five grades (0 to 4) according to the severity of atrophic changes, with three additional "plus" features: lacquer cracks, myopic macular neovascularization (MNV), and Fuchs spot. Based on this classification, PM is defined as myopic eyes with MM equal to or more severe than diffuse atrophy and/or eyes with posterior staphyloma.[9]

Deep learning (DL) architectures—particularly convolutional neural networks (CNNs)—have demonstrated remarkable efficiency in detecting ocular diseases from fundus photographs, including the diagnosis and classification of PM.[10,11] AI-powered DL systems not only offer automated classification, but also have the potential to enhance diagnostic efficiency, making them valuable tools for large-scale screening and clinical decision making (Figure 1).[12]

## FUNDUS-BASED PM DETECTION USING AI

As a cost-effective and noninvasive imaging modality widely used in routine eye care, fundus photography remains the primary choice for AI-driven PM detection. Its accessibility has facilitated the construction of large-scale datasets, enabling the development of robust CNN architectures. Additionally, the META-PM classification based on fundus imaging aligns well with AI model labeling requirements, further supporting automated PM detection.

A recent meta-analysis of 11 studies involving 165,787 eyes reported high diagnostic performance of AI-based tools in detecting MM and PM from fundus images, with an area under the summary receiver operator curve of 0.9905 and a pooled sensitivity of 0.959.[13] Several representative studies illustrate the evolution of this field—from simple binary classification (ie, MM vs non-MM) to more detailed grading across all five META-PM categories. In 2021, a retrospective multicohort study using 226,686 fundus images from nine multiethnic cohorts across six regions developed DL algorithms for classifying high myopia and MM.[12] In the same year, two studies demonstrated the ability of DL models to classify MM across categories 0 to 4 and detect "plus" lesions.[14,15]

The application of advanced computer vision techniques has enhanced the performance and efficiency of AI-based MM and PM detection. These innovations aim to reduce reliance on extensive manual annotations and explore the potential for fully automated diagnosis.

For example, Sun et al introduced a module that used the information of tessellated fundus and brightest image regions to assist in lesion localization using coarse-labeled images.[16] Yao et al developed DeepGraFT, a classification-and-segmentation co-decision model that first applies

image masking to isolate the region of interest.[17] This was followed by a binary classification for each MM category by Zhang et al that uses a technique known as self-supervised learning,[18] which refers to the development of generalist models capable of adapting to various downstream tasks with significantly less annotated data, demonstrating promising performance in automated MM diagnosis and grading.

## CHALLENGES TO AI IN PM SCREENING

### Establishing Clear, Unified Definitions of PM and MM in AI-Based Studies

One of the major challenges with AI-driven detection of PM and MM is inconsistency in their definitions. In the previously mentioned systematic review and meta-analysis, 17 studies were included in the systematic review, and only eight explicitly stated the use of the META-PM classification for MM identification, while the remaining studies did not clarify which classification system was applied.[13] This inconsistency complicates direct comparisons between models, as variations in diagnostic criteria can lead to significant differences in reported performance. Additionally, the lack of standardized definitions limits model generalization across diverse datasets and clinical settings. Future research should focus on establishing unified diagnostic criteria and standardized image labeling frameworks to enhance the reliability and applicability of AI models.

### Evaluating DL Algorithms in Diverse, Real-World Settings

Despite the increasing availability of publicly annotated datasets for PM (eg, the Pathologic Myopia Challenge dataset and the Singapore Epidemiology of Eye Diseases study dataset),[19-21] developing robust DL models for PM and MM diagnosis remains challenging. Variations in medical systems across different regions result in differences in the prevalence of PM and MM subtypes within study cohorts, affecting model performance and generalizability.

Recently, Qian et al introduced a publicly available dataset for MM diagnosis as part of the Myopic Maculopathy Analysis Challenge.[22] This dataset comprised 2,306 fundus images for MM classification, with seven teams participating in the competition. However, all fundus images were exclusively sourced from Chinese patients, which may limit the model's generalizability to other populations. Future research should expand datasets to include multiethnic populations and evaluate model performance in diverse clinical environments to ensure real-world applicability.

### Incorporating Multimodal Imaging

While the META-PM classification provides a standardized framework for identifying various stages of MM, it is solely based on fundus photographs, which presents potential diagnostic limitations. Fundus pigmentation variations among racial and ethnic groups can affect image interpretation, and other critical myopic macular pathologies, such as myopic traction maculopathy and dome-shaped macula, are not included. To address these gaps, an OCT-based classification has been proposed.[23]

Recent studies have demonstrated that DL models based on OCT images can reliably detect PM and its complications, including MNV, dome-shaped macula, and tractional changes such as retinoschisis, macular hole, and retinal detachment.[24-27] However, compared with fundus photography-based models, OCT-based AI research remains relatively limited. One major challenge is the lack of uniform diagnostic criteria and large annotated datasets, likely due to the complexity of PM and its diverse manifestations. Moreover, variations in OCT imaging systems used in real-world clinical practice pose additional barriers to the widespread implementation of these AI algorithms.

Despite the success of multimodal DL approaches in conditions such as glaucoma and AMD,[28-33] their application in PM remains underexplored. Future research should focus on integrating fundus photography, OCT, and other imaging modalities to enhance diagnostic accuracy and provide a more comprehensive assessment of PM-related complications.

Scan the QR code to view this article online, which includes a schematic that illustrates the META-PM classification system used for MM and PM diagnosis, the development pipeline of AI-DL algorithms, and the key challenges to clinical translation.

## CLINICAL TRANSLATION

In addition to challenges related to AI model development and evaluation, systemic barriers remain in the clinical translation of AI-based DL algorithms for PM and MM detection. First, the "black box" nature of many AI algorithms continues to hinder trust and acceptance among clinicians. This challenge has given rise to the field of explainable AI, which focuses on developing models that not only achieve high accuracy, but also provide transparent, interpretable reasoning behind their outputs,

thereby enhancing clinical trust and usability.[34]

The lack of rigorous clinical trials also limits our understanding of the true clinical value of these models—are they safe, effective, affordable, and relevant in the dynamic health care environment?[35] While many algorithms demonstrate high diagnostic performance in research settings, few have demonstrated meaningful clinical effect in real-world practice.[36] Furthermore, the seamless integration of AI tools into existing clinical workflows remains an obstacle. For example, it is unclear whether current PM and MM detection models are better suited for use in primary eye care settings or specialized settings, such as retinal clinics or high myopia centers. Determining the most appropriate clinical environment is essential for maximizing their utility and minimizing workflow disruption.

## ADDRESSING THESE CHALLENGES

Gunasekeran et al proposed a comprehensive framework known as the "5Ps: People, Policies, Processes, Platforms, and Products."[37] This framework outlines essential elements for the successful, large-scale deployment of medical AI solutions, such as those implemented in national diabetic retinopathy screening programs. Applying a similar framework to AI-based MM and PM detection systems may facilitate more effective, scalable, and sustainable integration into health care systems. ■

*Disclosure: The authors used ChatGPT in the original drafting of this article solely for language editing and grammar improvement. No content generation, data analysis, or interpretation was performed by AI.*


1. Iwase A, Araie M, Tomidokoro A, et al. Prevalence and causes of low vision and blindness in a Japanese adult population: the Tajimi Study. *Ophthalmology*. 2006;113(8):1354-1362.
2. Hsu WM, Cheng CY, Liu JH, Tsai SY, Chou P. Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology*. 2004;111(1):62-99.
3. Xu L, Wang Y, Li Y, et al. Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. *Ophthalmology*. 2006;113(7):1134e1-1134e11.
4. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036-1342.
5. Sankaridurg P, Tahhan N, Kandel H, et al. IMI impact of myopia. *Invest Ophthalmol Vis Sci*. 2021;62(5):2.
6. Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. *Am J Ophthalmol*. 2014;157(1):9-25e12.
7. Flitcroft DI, He M, Jonas JB, et al. IMI - defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Invest Ophthalmol Vis Sci*. 2019;60(3):M20-M30.
8. Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. *Am J Ophthalmol*. 2015;159(5):877-883e7.
9. Ohno-Matsui K, Lai TY, Lai CC, Cheung CM. Updates of pathologic myopia. *Prog Retin Eye Res*. 2016;52:156-187.
10. Li Z, Wang L, Wu X, et al. Artificial intelligence in ophthalmology: the path to the real-world clinic. *Cell Rep Med*. 18 2023;4(7):101095.
11. Du R, Ohno-Matsui K. Novel uses and challenges of artificial intelligence in diagnosing and managing eyes with high myopia and pathologic myopia. *Diagnostics (Basel)*. 2022;12(5):1210.
12. Tan TE, Anees A, Chen C, et al. Retinal photograph-based deep learning algorithms for myopia and a blockchain platform to facilitate artificial intelligence medical research: a retrospective multicohort study. *Lancet Digit Health*. 2021;3(5):e317-e329.
13. Prashar J, Tay N. Performance of artificial intelligence for the detection of pathological myopia from colour fundus images: a systematic review and meta-analysis. *Eye (Lond)*. 2024;38(2):303-314.
14. Du R, Xie S, Fang Y, et al. Deep learning approach for automated detection of myopic maculopathy and pathologic myopia in fundus images. *Ophthalmol Retina*. 2021;5(12):1235-1244.
15. Lu L, Ren P, Tang X, et al. AI-model for identifying pathologic myopia based on deep learning algorithms of myopic maculopathy classification and "plus" lesion detection in fundus images. *Front Cell Dev Biol*. 2021;9:719262.
16. Sun Y, Li Y, Zhang F, et al. A deep network using coarse clinical prior for myopic maculopathy grading. *Comput Biol Med*. 2023;154:106556.
17. Yao Y, Yang J, Sun H, et al. DeepGraFT: A novel semantic segmentation auxiliary ROI-based deep learning framework for effective fundus tessellation classification. *Comput Biol Med*. 2024;169:107881.
18. Zhang J, Xiao F, Zou H, Feng R, He J. Self-supervised learning-enhanced deep learning method for identifying myopic maculopathy in high myopia patients. *iScience*. 2024;27(8):110566.
19. Huazhu Fu, Fei Li, José Ignacio Orlando, et al. PALM: PAthoLogic Myopia Challenge. IEEE Dataport. July 8, 2019. Accessed July 16, 2025. ieee-dataport.org/documents/palm-pathologic-myopia-challenge
20. Fang H, Li F, Wu J, et al. Open fundus photograph dataset with pathologic myopia recognition and anatomical structure annotation. *Sci Data*. 2024;11(1):99.
21. Majithia S, Tham YC, Chee ML, et al. Cohort Profile: The Singapore epidemiology of eye diseases study (SEED). *Int J Epidemiol*. 2021;50(1):41-52.
22. Qian B, Sheng B, Chen H, et al. A competition for the diagnosis of myopic maculopathy by artificial intelligence algorithms. *JAMA Ophthalmol*. 2024;142(11):1006-1015.
23. Fang Y, Du R, Nagaoka N, et al. OCT-based diagnostic criteria for different Stages of myopic ,aculopathy. *Ophthalmology*. 2019;126(7):1018-1032.
24. Ye X, Wang J, Chen Y, et al. Automatic screening and identifying myopic maculopathy on optical coherence tomography images using deep learning. *Transl Vis Sci Technol*. 2021;10(13):10.
25. Li Y, Feng W, Zhao X, et al. Development and validation of a deep learning system to screen vision-threatening conditions in high myopia using optical coherence tomography images. *Br J Ophthalmol*. 2022;106(5):633-639.
26. Du R, Xie S, Fang Y, et al. Validation of soft lebels in developing deep learning algorithms for detecting lesions of myopic maculopathy from optical coherence tomographic images. *Asia Pac J Ophthalmol (Phila)*. 2022;11(3):227-236.
27. He X, Ren P, Lu L, et al. Development of a deep learning algorithm for myopic maculopathy classification based on OCT images using transfer learning. *Front Public Health*. 2022;10:1005700.
28. Kihara Y, Montesano G, Chen A, et al. Policy-driven, multimodal deep learning for predicting visual fields from the optic disc and OCT imaging. *Ophthalmology*. 2022;129(7):781-791.
29. Xiong J, Li F, Song D, et al. Multimodal machine learning using visual fields and peripapillary circular OCT scans in detection of glaucomatous optic neuropathy. *Ophthalmology*. 2022;129(2):171-180.
30. Bowd C, Belghith A, Rezapour J, et al. Multimodal deep learning classifier for primary open angle glaucoma diagnosis using wide-field optic nerve head cube scans in eyes with and without high myopia. *J Glaucoma*. 2023;32(10):841-847.
31. Anegondi N, Gao SS, Steffen V, et al. Deep learning to predict geographic atrophy area and growth rate from multimodal imaging. *Ophthalmol Retina*. 2023;7(3):243-252.
32. Spaide T, Jiang J, Patil J, et al. Geographic atrophy segmentation using multimodal deep learning. *Transl Vis Sci Technol*. 2023;12(7):10.
33. Yoo TK, Choi JY, Seo JG, Ramasubramanian B, Selvaperumal S, Kim DW. The possibility of the combination of OCT and fundus images for improving the diagnostic accuracy of deep learning for age-related macular degeneration: a preliminary experiment. *Med Biol Eng Comput*. 2019;57(3):677-687.
34. Hassija V, Chamola V, Mahapatra A, et al. Interpreting black-box models: a review on explainable artificial intelligence. *Cognitive Computation*. 2024;16(1):45-74.
35. Longhurst CA, Singh K, Chopra A, Atreja A, Brownstein JS. A call for artificial intelligence implementation science centers to evaluate clinical effectiveness. *NEJM AI*. 2024;1(8):AIp2400223.
36. Wolf RM, Channa R, Liu TYA, et al. Autonomous artificial intelligence increases screening and follow-up for diabetic retinopathy in youth: the ACCESS randomized control trial. *Nat Commun*. 2024;15(1):421.
37. Gunasekeran DV, Miller S, Hsu W, et al. National use of artificial intelligence for Eee screening in Singapore. *NEJM AI*. 2024;1(12):AIcs2400404.



**YINING WANG, MD**
- PhD Student, Department of Ophthalmology and Visual Science, Institute of Science Tokyo, Japan
- yiningwang241@gmail.com
- Financial disclosure: None

**TIEN YIN WONG, MBBS, MMED (OPHTH), MPH, PHD**
- Professor & Senior Vice Chancellor, Tsinghua Medicine, Beijing, China
- Director, Beijing Visual Science and Translational Eye Research Institute (BERI), School of Clinical Medicine, Tsinghua Medicine, Tsinghua University, Beijing, China
- Senior Advisor, Singapore National Eye Center, Singapore
- wongtienyin@tsinghua.edu.cn
- Financial disclosure: Consultant (Astellas, Bayer, Boehringer-Ingelheim, Carl Zeiss Meditec, Genentech/Roche, Novartis, Opthea, Plano, Quaerite Biopharm Research, Sanofi, Shanghai Henlius); Inventor/Patent Holder/Co-founder (EyRiS, Visre)

**KYOKO OHNO-MATSUI, MD, PHD**
- Professor, Department of Ophthalmology and Visual Science, Institute of Science Tokyo, Japan
- k.ohno.oph@tmd.ac.jp
- Financial disclosure: Consultant (CooperVision, Eye Rising, Santen, Topcon)

# PEARLS FOR IMAGING THE PERIPHERAL RETINA


A brief review of ultra-widefield OCT.

BY SZILÁRD KISS, MD, FASRS, AND PEYMAN RAZAVI, MD

OCT has become an indispensable tool in the monitoring of macular disease.[1] The introduction of spectral-domain OCT (SD-OCT) brought with it higher image resolution and faster acquisition and enabled volumetric imaging.[2] However, SD-OCT is limited in depth penetration.[2,3] The subsequent development of swept-source OCT (SS-OCT) addresses this limitation with a longer wavelength, while still allowing fast scan speeds. SS-OCT also improves visualization through media opacities such as gas and silicone oil.[3] While both technologies excel at posterior pole imaging, they are limited by the field of view (FOV). These systems now support longer linear scan lengths and montaging, expanding the ability to visualize pathology beyond the macula. Navigation, where OCT is guided by widefield (WF) fundus images to specific peripheral targets, has further extended OCT's utility into the periphery. As clinical workflows adapt, navigating OCT beyond the posterior pole is emerging as the new standard of care.

## CLASSIFICATION

Clearly defining WF and ultra-WF (UWF) is particularly important in OCT imaging, as some manufacturers label long posterior pole scans as WF or UWF despite limited anatomic reach. Retinal imaging nomenclature defines the FOV in relation to key anatomic landmarks. The agreed terminology is as follows[4]:

- WF imaging refers to views centered on the fovea that capture the retina in all four quadrants up to and including the vortex vein ampullae. This typically spans 60° to 100°, covering the midperiphery.
- UWF captures areas anterior to the vortex vein ampullae in all quadrants, extending into the far periphery. The field ranges from approximately 110° to 220°.
- Panretinal imaging aims to visualize the entire 360° retina from ora to ora. This requires a montage of multiple UWF images to cover the full circumference.
- Unlike en face images, OCT B-scans are not described in degrees of FOV. Instead, consensus recommends specifying linear scan length (mm), anatomic location (posterior pole, midperiphery, far periphery), and scan type (eg, 12-mm far-peripheral OCT).

## CLINICAL APPLICATIONS

Navigated WF SS-OCT enables detailed imaging of the midperipheral and peripheral neuroretina and vitreoretinal interface, improving detection of vision-threatening features such as retinal holes, tears, and subretinal fluid, with strong diagnostic correlation with histopathology.[5] One study demonstrated that navigated UWF SS-OCT reliably captured high-resolution images of peripheral retinal lesions, such as retinal holes with vitreous traction and subretinal fluid, and the OCT data proved clinically actionable in 38% of eyes.[6]

UWF OCT can help distinguish retinal detachment (RD) from degenerative retinoschisis when clinical findings are unclear.[7,8] There are reports of OCT revealing that some cases initially diagnosed as retinoschisis were actually RDs, and vice versa.[9,10] One study found that three of 18 presumed retinoschisis cases were actually

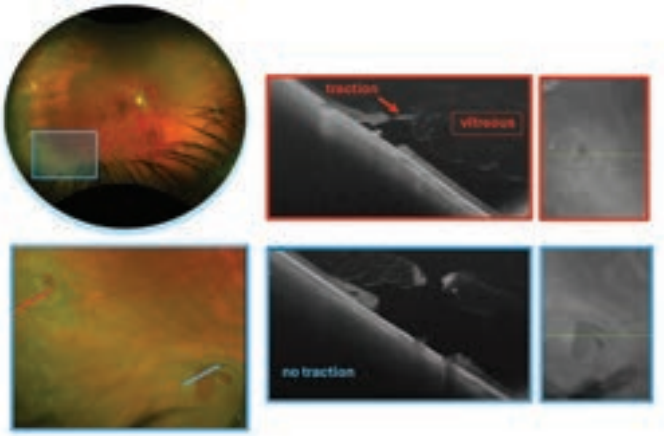



Figure 1. Two retinal tears in the same eye. UWF OCT shows vitreoretinal traction at one tear but not the other, highlighting how it can differentiate between similar-appearing lesions and guide risk-based management.

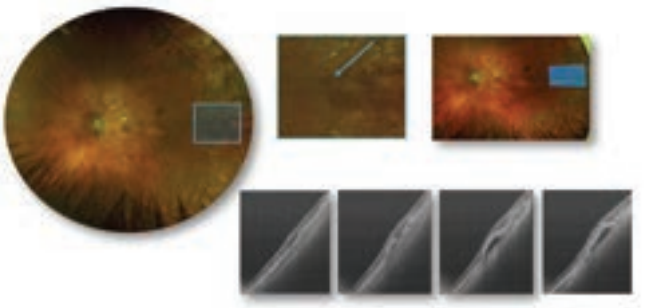


Figure 2. Peripheral choroidal neovascularization as seen on fundus imaging and UWF OCT.

RDs on peripheral OCT, while another study identified six such misdiagnoses in 53 eyes.[7,10] This differentiation is clinically important, as retinoschisis often does not require treatment, except in cases with retinal holes, which peripheral OCT can also detect.[11]

For rhegmatogenous RD, preoperative UWF OCT can localize the primary break by identifying a full-thickness defect in the retina or reveal the presence of peripheral vitreoretinal traction (Figure 1). Postoperatively, UWF OCT can assess retinal reattachment and look for persistent subretinal fluid or outer retinal folds.

OCT imaging after laser retinopexy and cryopexy for RD has demonstrated changes such as coagulative necrosis at laser spots and retinal pigment epithelium (RPE) separation under cryopexy scars in the early weeks, findings previously observed only in histologic studies.[12] Importantly, OCT through gas or silicone oil is possible with SS-OCT, allowing immediate postoperative imaging when a gas bubble is present. Thus, UWF OCT can verify if the retina is reattached under the bubble or oil and identify complications such as residual subretinal fluid pockets.

Peripheral abnormalities are frequently detected on UWF imaging in AMD, underscoring the need to evaluate beyond the macula.[13] UWF OCT enables identification of peripheral choroidal neovascularization and peripheral exudative hemorrhagic chorioretinopathy, which may present with hemorrhage, exudation, and subretinal fluid, features linked to increased risk of macular involvement (Figure 2).[14] Using UWF OCT, researchers have found that choroidal thinning in AMD extends into the periphery, while retinal thickness remains relatively stable, offering additional insight into disease extent.[15]

UWF OCT can distinguish peripheral choroidal melanoma from nevi, and subretinal fluid seen on OCT is a key risk factor for malignant transformation (Figure 3).[16] Additionally, SS-OCT can be used to image choroidal osteomas, capturing the full lesion and identifying associated neovascularization not easily seen with standard imaging due to RPE changes and lesion density.[17]

UWF OCT has been illuminating in the study of staphylomas and related macular deformities in pathologic

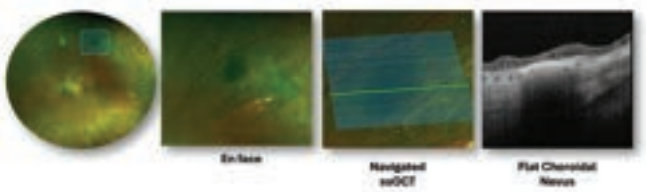


Figure 3. Clinicians can use UWF OCT imaging to capture peripheral choroidal nevi.

myopia. It has shown that posterior staphylomas are significantly less common in eyes with a dome-shaped macula, suggesting a dome-shaped macula may form independently.[18] Also, a dome-shaped macula is mostly associated with wide macular staphylomas and may represent a distinct posterior scleral curvature abnormality.[18] UWF OCT imaging also shows that age and axial length influence the shape of posterior staphylomas differently in wide and narrow types, suggesting distinct formation mechanisms for staphyloma subtypes.[19]

Another study demonstrated the utility of UWF OCT in high myopia for detecting and characterizing macular and paravascular retinoschisis, identifying key risk factors such as age, axial length, spherical equivalent, and high Gaussian curvature, which were associated with both the presence and severity of disease.[20] For clinicians, UWF OCT provides a means to track progressive elongation through changes in staphyloma geometry on serial scans and to detect peripheral pathology associated with high myopia. This helps differentiate various posterior segment findings (eg, true detachment vs schisis) and can guide timely interventions.

UWF OCT has potential applications in both the screening and monitoring of retinopathy of prematurity. It offers detailed views of the vascular-avascular junction and enables precise identification of neovascularization, especially extraretinal forms critical for staging.[21]

UWF OCT also shows promise in detecting retinoblastoma, including small peripheral tumors not visible on ophthalmoscopy.[22,23]

## LIMITATIONS AND CHALLENGES

UWF OCT faces several limitations, including optical distortion and reduced peripheral resolution from retinal curvature and oblique beam angles, leading to edge image degradation. WF scans can be technically challenging, at times requiring eccentric gaze, steady fixation, and dilation, increasing motion artifacts and shadowing, especially with media opacities.

High cost and large device size also hinder widespread use, although these issues are being mitigated by advances in software, automation, and training.

## FUTURE DIRECTIONS

Peripheral retinal imaging is rapidly evolving. Faster OCT systems will enable high-resolution WF scans with fewer

*(Continued on page 31)*

Triesence
(triamcinolone acetonide injectable suspension)
40 mg/mL

# You asked for it, Harrow® BROUGHT IT BACK FOR YOU!

**Proven and FDA-Approved!**

**Triesence®** is the **first & only** preservative-free synthetic steroid that is FDA-approved for visualization during vitrectomy, uveitis, and for the treatment of ocular inflammatory conditions that are unresponsive to topical corticosteroids.[1]


## Preservative-Free

TRIESENCE is preservative-free, which reduces the risk of non-infectious endophthalmitis which can be associated with benzyl alcohol.*[2]

Visit us at triesencehcp.com to learn more.

*There is a general risk of infectious endophthalmitis development from intravitreal injection procedures.

### Visualization during vitrectomy

In the clinical studies, TRIESENCE was proven to be highly effective at enhancing visualization of posterior tissues and vitreous during vitrectomy.[3]

### Uveitis

TRIESENCE improves visual acuity and reduces macular thickness in eyes with macular edema from various causes.[4]

### Safe for the operating room

TRIESENCE is terminally sterilized and comes in a vial with a sterile exterior, making it ideal for use in the operating room.[1]

## APPROVED USE

TRIESENCE® Suspension is indicated for:

- Treatment of the following ophthalmic diseases: sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
- Visualization during vitrectomy.

## IMPORTANT SAFETY INFORMATION

### Contraindications

- TRIESENCE® Suspension is contraindicated in patients with systemic fungal infections.
- TRIESENCE® Suspension is also contraindicated in patients with hypersensitivity to corticosteroids or any component of TRIESENCE® Suspension. Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.

### Warnings and Precautions

- *TRIESENCE® is a suspension; it should not be administered intravenously.*
- *Ophthalmic effects: May include cataracts, infections, and glaucoma. Monitor intraocular pressure.*
- *Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and hyperglycemia: Monitor patients for these conditions and taper doses gradually.*
- *Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection.*
- *Elevated blood pressure, salt and water retention, and hypokalemia: Monitor blood pressure and sodium, potassium serum levels.*
- *GI perforation: Increased risk in patients with certain GI disorders.*
- *Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis.*
- *Decreases in bone density: Monitor bone density in patients receiving long term corticosteroid therapy.*
- *Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids.*
- *Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy.*
- *Use in pregnancy: Fetal harm can occur with first trimester use.*
- *Weight gain: May cause increased appetite.*

### Adverse Reactions

- Based on a review of the available literature, the most commonly reported adverse events following ocular administration of triamcinolone acetonide were elevated intraocular pressure and cataract progression. These events have been reported to occur in 20-60% of patients.
- Less common reactions occurring in up to 2% of patients include: endophthalmitis (infectious and non-infectious), hypopyon, injection site reactions (described as blurring and transient discomfort), glaucoma, vitreous floaters, detachment of retinal pigment epithelium, optic disc vascular disorder, eye inflammation, conjunctival hemorrhage and visual acuity reduced. Cases of exophthalmos have also been reported.

### Drug Interactions

- *Anticoagulant Agents* – Corticosteroids may enhance or diminish the anticoagulant effect of anticoagulant agents. Coagulation indices should be monitored.
- *Antidiabetic Agents* – Corticosteroids may increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required.
- *CYP 3A4 Inducers and Inhibitors* – CYP 3A4 inducers and inhibitors may respectively increase or decrease clearance of corticosteroids, necessitating dose adjustment.
- *NSAIDs* – Concomitant use of NSAIDS, including aspirin and salicylates, with a corticosteroid may increase the risk of GI side effects.

For additional Important Safety Information about TRIESENCE® Suspension, please see the Full Prescribing Information at triesencehcp.com.

HARROW™
Your patients. Our purpose.

**References: 1.** TRIESENCE Prescribing Information. Harrow IP, LLC; 2023. **2.** Maia M, Farah ME, Belfort RN, *et al* Effects of intravitreal triamcinolone acetonide injection with and without preservative. *British Journal of Ophthalmology* 2007;91:1122-1124. **3.** Dyer, David Md; Callanan, David Md; Clinical Evaluation Of The Safety And Efficacy Of Preservative-Free Triamcinolone (Triesence® [Triamcinolone Acetonide Injectable Suspension] 40 Mg/Ml) For Visualization During Pars Plana Vitrectomy. Retina 29(1):P 38-45, January 2009. | Doi: 10.1097/Iae.0b013e318188c6e2 **4.** Data on file.

# Triesence®
## (triamcinolone acetonide injectable suspension) 40 mg/mL

**BRIEF SUMMARY – PLEASE SEE THE TRIESENCE® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE:**

TRIESENCE® is a synthetic corticosteroid indicated for:

- Treatment of the following ophthalmic diseases: sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
- Visualization during vitrectomy.

**CONTRAINDICATIONS**

- Patients with systemic fungal infections.
- Hypersensitivity to triamcinolone or any component of this product.

**DOSAGE AND ADMINISTRATION:**

- Initial recommended dose for all indications except visualization: 4 mg (100 microliters of 40 mg/mL suspension) with subsequent dosage as needed over the course of treatment.
- Recommended dose for visualization: 1 to 4 mg (25 to 100 microliters of 40 mg/mL suspension) administered intravitreally.

**WARNINGS AND PRECAUTIONS**

- TRIESENCE® is a suspension; it should not be administered intravenously.
- Ophthalmic effects: May include cataracts, infections, and glaucoma. Monitor intraocular pressure.
- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia: Monitor patients for these conditions and taper doses gradually.
- Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection.
- Elevated blood pressure, salt and water retention, and hypokalemia: Monitor blood pressure and sodium, and potassium serum levels.
- GI perforation: Increased risk in patients with certain GI disorders.
- Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis.
- Decreases in bone density: Monitor bone density in patients receiving long term corticosteroid therapy.
- Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids.
- Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy.
- Use in pregnancy: Fetal harm can occur with first trimester use.
- Weight gain: May cause increased appetite.

**ADVERSE REACTIONS**

- Based on a review of the available literature, the most commonly reported adverse events following ocular administration of triamcinolone acetonide were elevated intraocular pressure and cataract progression. These events have been reported to occur in 20-60% of patients.
- Less common reactions occurring in up to 2% of patients include: endophthalmitis (infectious and non-infectious), hypopyon, injection site reactions (described as blurring and transient discomfort), glaucoma, vitreous floaters, detachment of retinal pigment epithelium, optic disc vascular disorder, eye inflammation, conjunctival hemorrhage and visual acuity reduced. Cases of exophthalmos have also been reported.

**DRUG INTERACTIONS**

- *Anticoagulant Agents* – Corticosteroids may enhance or diminish the anticoagulant effect of anticoagulant agents. Coagulation indices should be monitored.
- *Antidiabetic Agents* – Corticosteroids may increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required.
- *CYP 3A4 Inducers and Inhibitors* – CYP 3A4 inducers and inhibitors may respectively increase or decrease clearance of corticosteroids, necessitating dose adjustment.
- *NSAIDs* – Concomitant use of NSAIDS, including aspirin and salicylates, with a corticosteroid may increase the risk of GI side effects.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary

Two prospective case control studies showed decreased birth weight in infants exposed to maternal corticosteroids in utero. Triamcinolone acetonide was shown to be teratogenic in rats, rabbits, and monkeys at inhalation doses of 0.02 mg/kg and above and in monkeys, triamcinolone acetonide was teratogenic at an inhalation dose of 0.5 mg/kg (1/4 and 7 times the recommended human dose). Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

**Nursing Mothers**

Corticosteroids are secreted in human milk. The risk of infant exposure to steroids through breast milk should be weighed against the known benefits of breastfeeding for both the mother and baby.

**Pediatric Use**

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. The adverse effects of corticosteroids in pediatric patients are similar to those in adults.

**Geriatric Use**

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience with triamcinolone has not identified differences in responses between the elderly and younger patients.

**PATIENT COUNSELING INFORMATION**

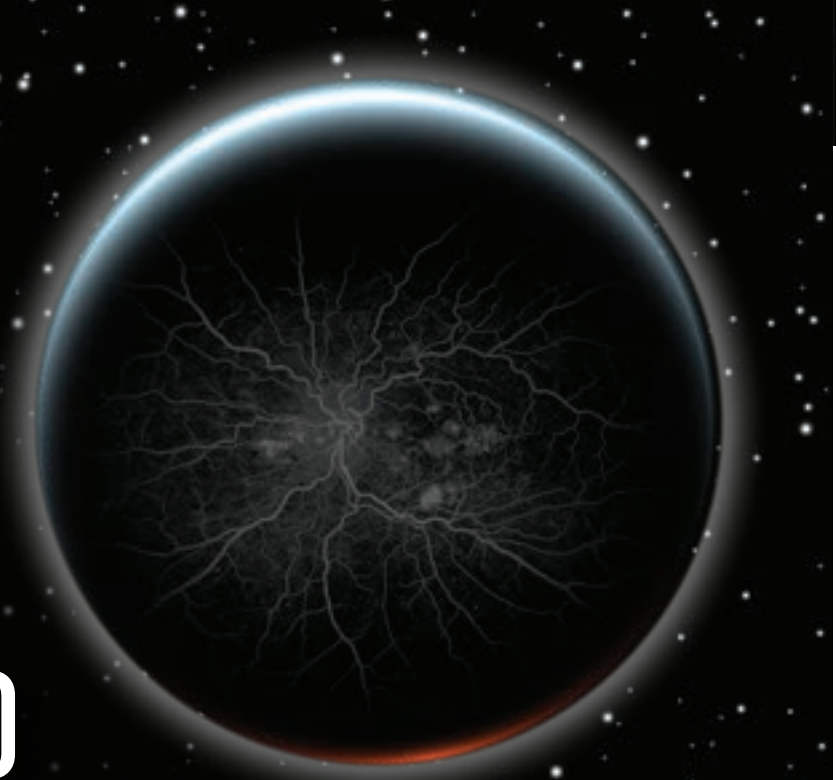
Patients should discuss with their physician if they have had recent or ongoing infections or if they have recently received a vaccine.

Patients should be advised of common adverse reactions that could occur with corticosteroid use such as elevated intraocular pressure, cataracts, fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.

HARROW™

TRI-00004 06/24

# MODERN DIABETES CARE: WHAT YOU NEED TO KNOW



## The changing landscape of systemic diabetes care is affecting ocular complications such as diabetic retinopathy.

By Samaantar Joshi, BS; Khiem Sy Nguyen, BS; Jonathan B. Lin, MD, PhD; and Ehsan Rahimy, MD




With new therapies and devices changing diabetes care, there is growing interest in how they affect ophthalmic outcomes for patients with diabetic retinopathy (DR). Here, we discuss continuous glucose monitoring (CGM) devices, next-generation systemic pharmacotherapy, and digital diabetes management platforms (DDMPs).

### CONTINUOUS GLUCOSE MONITORING

Managing diabetes requires maintaining a strict diet and regularly monitoring blood glucose. Today, CGM devices are minimally invasive monitors that can be implanted subcutaneously to monitor blood glucose levels in real time.

### AT A GLANCE

- Research shows that the use of continuous glucose monitoring devices is linked with lower odds of progression to diabetic retinopathy (DR) and proliferative DR.
- The DR-related adverse effects of new therapies are still under investigation, and various studies have yielded mixed, sometimes conflicting, findings.
- Digital diabetes management platforms integrate telemedicine, personalized coaching, connected technologies, and glycemic monitoring to help patients manage their diabetes.

For example, the G6 CGM device (Dexcom) was shown to enable more precise insulin dose adjustment and improve glycemic control.[1] Other positive effects, such as prolonged duration within the target glycemic range and reduced hypoglycemic events, were also seen.[1]

CGM can also improve DR management. One cohort study examined the odds of patients with type 1 diabetes developing DR and proliferative DR (PDR) when using CGM, insulin pumps, or both.[2] CGM use was linked with lower odds of progression to DR and PDR. Additionally, CGM with an insulin pump was linked with lower odds of PDR when compared with no CGM use.[2] Overall, CGM use was associated with slower disease progression, even after controlling for other health and demographic factors.

Another study examined whether metrics obtained with CGM were associated with DR severity. Data obtained from the FreeStyle Libre Pro CGM device (Abbott Japan) showed that intra- and inter-day glucose variability in patients with diabetes was significantly associated with DR severity, even after adjusting for risk factors. Thus, CGM may aid in identifying patients at the highest risk for developing diabetic eye disease, reinforcing its utility in diabetes care.[3]

As enthusiasm for and acceptance of CGM continues to grow, we have seen further expansion of its capabilities and integration into modern diabetes management. For example, a CGM device can now be paired with a smart insulin pump in a closed-loop system to automatically adjust insulin delivery. This tandem unit helps regulate blood glucose levels in real time, essentially functioning as an artificial pancreas.[4]

Recently, access to these devices have improved with the FDA approval of the first over-the-counter CGM, the Stelo Glucose Biosensor System (Dexcom).[5] Furthermore, various health startup companies are now using CGM technology for patients without diabetes to help users better understand how diet and lifestyle choices affect their glycemic levels.[6]

## NEXT-GENERATION SYSTEMIC PHARMACOTHERAPY

In the past decade, FDA-approved novel classes of therapies for diabetes have expanded the armamentarium of diabetic pharmacotherapy. Although some of these newer treatments have been praised for their protective effects on mortality, cardiovascular, and renal outcomes,[7] DR-related adverse effects are still under investigation, and various studies have yielded mixed, sometimes conflicting, findings.

The introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has been met with significant positive reception due to their ability to significantly reduce hemoglobin A1c, major adverse cardiovascular events, and weight.[8] In the SUSTAIN-6 trial investigating the cardiovascular safety of semaglutide, patients receiving the study drug experienced fewer cardiovascular adverse effects but significantly more retina-related complications, including vitreous hemorrhage, blindness, and conditions requiring additional ocular treatments.[9]

However, limitations of the study, such as a short follow-up time, call into question these adverse ocular findings. Notably, the worsened/increased DR events have yet to be corroborated by other randomized controlled trials. In addition, a dilated fundus examination was not required in the study, and the classification of DR status was not uniform at the study onset; thus, patients with PDR or diabetic macular edema (DME) at baseline were likely included, rendering any true tabulation of vision-threatening complications during the study nebulous.[10] Finally, SUSTAIN-6 was a cardiovascular outcome trial, and DR was not a primary outcome measure. The 5-year FOCUS trial is now investigating the long-term effects of semaglutide on DR in approximately 1,500 patients with type 2 diabetes.[11] (For more on this topic, see *GLP-1 Receptor Agonists and the Eye* on page 28.)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have also been gaining significant popularity in the medical community largely due to their nephroprotective effects. Mechanistically, SGLT2 inhibitors prevent glucose reabsorption in the renal proximal tubule of the kidney, resulting in increased urinary glucose excretion.[12]

Several studies have found diminished DR risk and slower DR progression with SGLT2 inhibitor use in patients with type 2 diabetes.[13-16] These observations were corroborated by an aggregate electronic health record (EHR) retrospective clinical cohort study (n = 6,481) using the TriNetX Research Network. Patients on GLP-1 RA monotherapy had significantly higher rates of PDR progression and new-onset DME compared with those on SGLT2 inhibitor monotherapy.[17] In contrast, a 2024 retrospective cohort study found no significant difference in the risk of developing vision-threatening DR between patients newly initiated on SGLT2 inhibitors versus other non-insulin diabetic medications.[18]

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that degrades endogenous GLP-1. This class of inhibitors mechanistically increases GLP-1 bioavailability and downstream insulin secretion. A recent analysis in Taiwan revealed that patients with newly diagnosed diabetes who were treated with a DPP-4 inhibitor demonstrated an increased risk of DR compared with those who were treated with a sulfonylurea.[19] One possible explanation for this is DPP-4's role in cleaving other endogenous substrates, including stromal cell-derived factor-1 alpha (SDF-1$\alpha$). DPP-4 inhibitors, therefore, may increase levels of SDF-1$\alpha$, which has been shown to promote pathologic angiogenesis in animal models of DR.[20] Yet, not all evidence supports a causal relationship. For instance, a 2024 meta-analysis of seven real-world studies found no association between DPP-4 inhibitors and DR risk, suggesting the mechanistic concerns may not translate to clinical harm.[21]

While there have been ample retrospective observational

# THE DIABETES PIPELINE IN 2025 REMAINS ACTIVE

BY PETER K. KAISER, MD

Diabetic eye disease—diabetic retinopathy (DR) and diabetic macular edema (DME)—affects 9.6 million Americans, with 1.8 million Americans experiencing vision-threatening DR.[1] Globally, 18.8 million patients have vision-threatening DR; that figure is expected to grow to 44.8 million by 2045.[2]

The good news: the pipeline for treatments remains robust. Researchers have identified dozens of potential targets. Perhaps even more exciting: outside-the-box approaches to drug administration mean that more comfortable, accessible, and effective treatments could reduce treatment burden and improve outcomes. Just think what it could mean for our patients if, rather than visiting (and sometimes not visiting) our clinics for routine injections, they could swallow a pill or inject a subcutaneous therapy from home.

For this inaugural edition of the diabetes pipeline poster, we have organized the various treatments and pipeline candidates by route of administration rather than by therapeutic target. In some cases, a single therapeutic approach is under investigation via multiple routes of administration. Take the tyrosine kinase inhibitor vorolanib, for example. Four different formulations of this molecule are under investigation for the treatment of diabetic eye disease: two are intravitreal injections, one is an oral agent, and one is an eye drop.

On the right side of the poster, I called out the three routes of administration for gene therapy, listing the benefits and drawbacks of each approach. For now, there is only a single gene therapy under investigation for DR. I hope that by next year we have more candidates to populate that list.

Observant readers will recognize the cell surface on the left side of the poster (and the legend showing various receptors at the base of the poster) from the poster covering the wet age-related macular degeneration pipeline *Retina Today* released earlier this year. These two posters are siblings, which explains why they look alike. To view the poster on age-related macular degeneration, scan the QR code above. ■

**If you have a drug candidate that you think should be on next year's version of the poster, reach out to me at pkkaiser@gmail.com or contact Cara Deming, Executive Director of Special Projects at Bryn Mawr Communications, at cdeming@bmctoday.com.**

1. Lundeen EA, Burke-Conte Z, Rein DB, et al. Prevalence of diabetic retinopathy in the US in 2021. *JAMA Ophthalmol*. 2023;141(8):747-754.
2. Teo ZL, Tham YC, Yu M, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. *Ophthalmology*. 2021;128(11):1580-1591.

**PETER K. KAISER, MD**
- Medical advisor, *Retina Today*
- Chaney Family Endowed Chair in Ophthalmology Research; Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine; consulting surgeon in the vitreoretinal department at the Cole Eye Institute, Cleveland Clinic; founding director of the Cole Eye Reading Center, all in Cleveland, Ohio
- pkkaiser@gmail.com
- Financial disclosures: Advisory Board and Consultant (AbbVie, Alexion, Alkeus, Allgenesis, Alzheon, Amaros, Annexon Biosciences, AsclepiX, Astellas, Augen Therapeutics, Aviceda, Bayer, Bausch and Lomb, Beacon Therapeutics (AGTC), Biogen Idec, Carl Zeiss Meditec, Celltrion Healthcare Co., Complement Therapeutics, Endogena Therapeutics, Frontera Therapeutics, Galimedix, Innovent, Invirsa, iRenix, Isarna, Janssen, jCyte, Kanaph Therapeutics, Kanghong, Kera Therapeutics, Kriya Therapeutics, Movu/Santec, Nanoscope Therapeutics, Ocugenix, Oculis, Omeros, Osanni Bio, Panther Pharmaceuticals, Ray Therapeutics, RegenxBio, Resonance Medicine Inc., Restore Vision, Retinal Sciences, ReVana, Revopsis, Roivant, Samsung Bioepis, Sandoz, SGN Nanopharma Inc., SmileBiotek Zhuhai Ltd, Stealth Biotherapeutics, Stuart, Sudo Biosciences, Sustained Nano Systems, Théa, Tilak, Unity Biotechnology, Vanotech, VisgenX); Board of Directors (AAVAntgarde Bio); Employee

series and aggregate EHR-based analyses on the effects of these novel therapeutic classes on the retinal microcirculation, we still lack formal prospective evaluations in randomized clinical trials. Ongoing research efforts are necessary to better understand the multifactorial effects of these novel systemic agents on the development and progression of DR.

## DIGITAL PLATFORMS

DDMPs integrate telemedicine, personalized coaching, connected technologies, and glycemic monitoring to help patients manage their diabetes. Many companies have developed their own DDMP (eg, Virta Health, Livongo Health, Omada Health, and Glooko, to name a few), each with its own unique approach to personalized diabetes care.

Virta Health delivers an individualized approach to carbohydrate intake and nutritional ketosis. In the company's 5-year study, 122 patients participated in a continuous care intervention via telemedicine that included counseling on a strict, very low-carbohydrate diet with nutritional ketosis. Maintenance of hemoglobin A1c less than 6.5% with either no medication or metformin alone was achieved in 32.5% of the patients who completed the study, highlighting the value of telemedicine-based interventions.[22] However, nearly 30% of patients who initially consented to participate in the study dropped out before the 5-year mark, emphasizing that these rigorous interventions are not feasible for all patients.

Livongo Health provides a self-monitoring blood glucose device with real-time glucose readings. Abnormal readings trigger an alert to a certified diabetes educator who provides resources or escalates to a consultation with a provider or emergency services. In a 2021 study, patients using Livongo Health and a cohort receiving specialized care from the University of Massachusetts Medical Center Diabetes Center of Excellence had similar reductions in hemoglobin A1c, suggesting the digital tool could be an alternative for those who do not have access to specialty clinics.[23]

Omada Health focuses on providing a structured curriculum and peer-group support. The platform helps patients manage their diabetes and other chronic conditions by combining data from their CGM, weekly goals, lab tests, and other sources and then sending it to the patient's primary care provider. Of patients who used the Omada Health app, 76% met their hemoglobin A1c reduction goal and experienced a 1.17 $kg/m^2$ mean reduction in body mass index over 12 months.[24,25]

## CARE FOR THE WHOLE PATIENT

It is essential that retina specialists be knowledgeable about the changing landscape of modern systemic diabetes care to best care for their patients with DR. Future studies that investigate the ongoing effects of these new therapies and devices on DR will help us better tailor treatment to the individual patient. ■


1. Manov AE, Chauhan S, Dhillon G, et al. The effectiveness of continuous glucose monitoring devices in managing uncontrolled diabetes mellitus: a retrospective study. *Cureus*. 2023;15(7):e42545.
2. Liu TYA, Shpigel J, Khan F, et al. Use of diabetes technologies and retinopathy in adults with type 1 diabetes. *JAMA Netw Open*. 2024;7(3):e240728.
3. Wakasugi S, Mita T, Katakami N, et al. Associations between continuous glucose monitoring-derived metrics and diabetic retinopathy and albuminuria in patients with type 2 diabetes. *BMJ Open Diabetes Res Care*. 2021;9(1):e001923.
4. NIH. Artificial pancreas. National Institute of Diabetes and Digestive and Kidney Diseases. 2021. Accessed July 11, 2025. bit.ly/45dkE7z
5. Stelo by Dexcom first glucose biosensor cleared by FDA as over-the-counter [press release]. Dexcom. March 5, 2024. Accessed July 8, 2025. bit.ly/3IFXQEM
6. Klonoff DC, Nguyen KT, Xu NY, Gutierrez A, Espinoza JC, Vidmar AP. Use of continuous glucose monitors by people without diabetes: an idea whose time has come? *J Diabetes Sci Technol*. 2023;17(6):1686-1697.
7. Drake T, Landsteiner A, Langsetmo L, et al. Newer pharmacologic treatments in adults with type 2 diabetes: a systematic review and network meta-analysis for the American College of Physicians. *Ann Intern Med*. 2024;177(5):618-632.
8. Zheng Z, Zong Y, Ma Y, et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Signal Transduct Target Ther*. 2024;9(1):234.
9. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
10. Simó R, Hernández C. GLP-1R as a target for the treatment of diabetic retinopathy: friend or foe?. *Diabetes*. 2017;66(6):1453-1460.
11. A research study to look at how semaglutide compared to placebo affects diabetic eye disease in people with type 2 diabetes (FOCUS). clinicaltrials.gov/study/NCT03811561
12. Sha W, Wen S, Chen L, Xu B, Lei T, Zhou L. The role of SGLT2 inhibitor on the treatment of diabetic retinopathy. *J Diabetes Res*. 2020;2020:8867875.
13. Barkhordari S, Ghaffariyan S, Banei F, et al. The association between the utilization of SGLT2 inhibitors and diabetic retinopathy; a systematic review and meta-analysis of cohort studies. *J Nephropharmacol*. 2024;13(2):e12688-e12688.
14. Ma Y, Lin C, Cai X, et al. The association between the use of sodium glucose cotransporter 2 inhibitor and the risk of diabetic retinopathy and other eye disorders: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol*. 2022;15(7):877-886.
15. Yen FS, Wei JC, Yu TS, Hung YT, Hsu CC, Hwu CM. (2023). Sodium-glucose cotransporter 2 inhibitors and risk of retinopathy in patients with type 2 diabetes. *JAMA Netw Open*. 2023 Dec 1;6(12):e2348431.
16. Huang ST, Bair PJ, Chang SS, et al. Risk of diabetic retinopathy in patients with type 2 diabetes after SGLT-2 inhibitors: a nationwide population cohort study. *Clin Pharmacol Ther*. 2024;115(1):95-103.
17. Wai KM, Mishra K, Koo E, et al. Impact of GLP-1 agonists and SGLT-2 inhibitors on diabetic retinopathy progression: an aggregated electronic health record data study. *Am J Ophthalmol*. 2024;265:39-47.
18. Nadelmann JB, Miller CG, McGeehan B, Yu Y, VanderBeek BL. SGLT2 inhibitors and diabetic retinopathy progression. *Graefes Arch Clin Exp Ophthalmol*. 2024;262(3):753-758.
19. Li YC, Kuan YH, Yang Y, et al. Association of long-term use of dipeptidyl peptidase-4 inhibitors with the risk of diabetic retinopathy in patients with diabetes mellitus: a real-world evidence study. *Front Pharmacol*. 2025;16:1518545.
20. Butler JM, Guthrie SM, Koc M, et al. SDF-1 is both necessary and sufficient to promote proliferative retinopathy. *J Clin Invest*. 2005;115(1):86-93.
21. Wang M, Lu J, Dong J. Association between dipeptidyl peptidase-4 inhibitor use and diabetic retinopathy: a systematic review and meta-analysis of real-world studies. *BMC Ophthalmol*. 2024;24(1):272.
22. McKenzie AL, Athinarayanan SJ, Van Tieghem MR, et al. 5-year effects of a novel continuous remote care model with carbohydrate-restricted nutrition therapy including nutritional ketosis in type 2 diabetes: An extension study. *Diabetes Res Clin Pract*. 2024;217:111898.
23. Amante DJ, Harlan DM, Lemon SC, et al. Evaluation of a diabetes remote monitoring program facilitated by connected glucose meters for patients with poorly controlled type 2 diabetes: randomized crossover trial. *JMIR Diabetes*. 2021;6(1):e25574.
24. Berthoumieux A, Linke S, Merry M, Megliola A, Juusola J, Napoleone J. Long-term results of a digital diabetes self-management and education support program among adults with type 2 diabetes: a retrospective cohort study. *Sci Diabetes Self Manag Care*. 2024;50(1):19-31.
25. Omada Health joins Amazon's Health Condition Programs as launch partner [press release]. Omada Health. January 8, 2024. Accessed July 8, 2025. bit.ly/46hULEP



**SAMAANTAR JOSHI, BS**
- Medical Student, California Health & Sciences University, Clovis, California
- Financial disclosure: None

**KHIEM SY NGUYEN, BS**
- Medical Student, Western University of Health Sciences, Pomona, California
- Research Assistant, Byers Eye Institute, Department of Ophthalmology, Stanford University School of Medicine, Palo Alto, California
- Financial disclosure: None

**JONATHAN B. LIN, MD, PHD**
- Vitreoretinal Surgery Fellow, Byers Eye Institute, Department of Ophthalmology, Stanford University School of Medicine, Palo Alto, California
- Financial disclosure: None

**EHSAN RAHIMY, MD**
- Vitreoretinal Surgeon, Vitreoretinal Surgery and Disease, Department of Ophthalmology, Palo Alto Medical Foundation, Palo Alto, California
- Adjunct Clinical Assistant Professor, Byers Eye Institute, Department of Ophthalmology, Stanford University School of Medicine, Palo Alto, California
- Editorial Advisory Board Member, *Retina Today*
- erahimy@gmail.com
- Financial disclosure: None

# GLP-1 RECEPTOR AGONISTS AND THE EYE

Researchers are working to understand the effects of these popular new therapies on ocular structures.

By Suraj Bala, BS; Julia H. Joo, MD; and Aleksandra V. Rachitskaya, MD



Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) promote physiologic glucose-dependent insulin release.[1] Originally FDA-approved for type 2 diabetes, GLP-1 RAs also lead to sustained weight loss and have revolutionized diabetes and obesity management.[2,3] Furthermore, several cardiovascular outcome trials (CVOT) suggest GLP-1 RAs confer a mortality benefit, with significant reductions in major adverse cardiovascular events, all-cause mortality, heart failure severity, and worsening kidney function.[4]

GLP-1 RAs also exert antiinflammatory and neuroprotective benefits on the central nervous system, retina, and other ocular structures,[5-8] and research shows reduced risk of neurodegenerative diseases such as Alzheimer and Parkinson dementia.[9-12] Many studies have investigated the role of GLP-1 RAs on the risk of ophthalmic diseases, including diabetic retinopathy (DR), glaucoma, AMD, idiopathic intracranial hypertension (IIH), and nonarteritic anterior ischemic optic neuropathy (NAION). Here, we provide an overview of the effect of GLP-1 RAs on ophthalmic diseases.

## DIABETIC RETINOPATHY

The relationship between DR and GLP-1 RAs remains controversial. Concern was initially raised by the findings of the SUSTAIN-6 CVOT that suggested the risk of DR complications was elevated in patients using semaglutide compared with placebo (3.0% vs 1.8%, $P = .02$).[13] Two meta-analyses of other GLP-1 RA CVOTs found that GLP-1 RAs

## AT A GLANCE

- Originally FDA-approved for type 2 diabetes, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) also lead to sustained weight loss and have revolutionized diabetes and obesity management.
- Many studies have investigated the relationship between GLP-1 RAs and ophthalmic diseases, including diabetic retinopathy, glaucoma, AMD, idiopathic intracranial hypertension, and nonarteritic anterior ischemic optic neuropathy.

were associated with greater rates of DR progression, but both studies found that the effect was driven by the extent of hemoglobin A1c reduction, rather than the medications themselves.[14,15] Another meta-analysis of 93 clinical trials showed that GLP-1 RAs increased the risk of early-stage DR compared with placebo, with this effect being driven by albiglutide in particular.[16]

A challenge of comparing data between CVOTs is the inconsistency in the protocols for accurately detecting retinal changes. Not all studies required dilated fundus examinations or retinal imaging, and they differed in inclusion criteria that would affect risk for disease progression. For example, while the SUSTAIN-6 study included patients with proliferative DR (PDR) and diabetic macular edema (DME), other CVOTs, such as PIONEER 6, did not.[17]

Moreover, the effects of GLP-1 RAs on DR have been explored in many retrospective large database studies, which have also yielded conflicting results. Some national electronic health record (EHR) database studies showed an elevated risk of DR development or progression.[18,19] Two such studies received letters to the editor with concerns that either the study design was not rigorous enough or the dataset used was not appropriate for ophthalmic questions.[20,21]

Others showed a protective effect of GLP-1 RAs on DR progression. Zheng et al showed that GLP-1 RA use was associated with a lower risk of DR in 2,390 patients in a national Swedish registry using both observational and genetic data.[22] Several other studies showed that there was no significant relationship between GLP-1 RAs and DR worsening, including one study by Joo et al in which manual review of the data was conducted to ensure accuracy in the ICD coding used to determine outcomes.[23-25]

To resolve this confusion, the prospective FOCUS trial was initiated in 2019. The trial is studying the effects of semaglutide on DR complications in 1,500 patients with type 2 diabetes and is estimated to be completed in 2027.[26]

## GLAUCOMA

Numerous studies have assessed the relationship between GLP-1 RAs and glaucoma, and most have shown that GLP-1 RAs confer a protective effect. For example, Muayad et al compared 61,998 patients with diabetes using GLP-1 RAs with metformin users in the US Collaborative Network of the TriNetX EHR database to calculate the risk of developing ocular hypertension or primary open-angle glaucoma, requiring topical glaucoma medication, or requiring laser trabeculoplasty.[27] At the 1-, 2-, and 3-year timepoints, they found that the GLP-1 RA cohort had a significantly lower risk of all three outcomes compared with metformin users.[27]

In a case-control study, Niazi et al compared 1,737 patients with glaucoma with 8,685 controls without glaucoma.[28] They found that GLP-1 RA use was associated with a lower risk of incident glaucoma (hazard ratio [HR] = .81), with the risk decreasing even further when GLP-1 RAs were used for longer than 3 years (HR = .71). However, a cohort study using TriNetX found that sodium-glucose co-transporter 2 inhibitors also significantly decreased the risk of new glaucoma diagnosis compared with GLP-1 RAs (HR = .932).[29]

In a systematic review and meta-analysis pooling these and other studies, Amaral et al found that the risk of glaucoma development was lower in patients taking GLP-1 RAs (HR = .71) compared with controls.[30] These clinical findings are supported by similar findings in basic science studies.[31]

## AMD

Only two studies thus far have reported on the association between GLP-1 RAs and AMD. Allan et al used the TriNetX EHR platform to evaluate the risk of developing dry and wet AMD compared with controls in 9,669 patients taking GLP-1 RA medications.[32] Included patients were matched for age, sex, race and ethnicity, cardiovascular diseases, DR severity (including PDR and DME status), history of tobacco use, body mass index, and hemoglobin A1c percentage. The authors found that GLP-1 RA use was associated with a significantly decreased risk of developing dry AMD compared with patients taking metformin (HR = .68), insulin (HR = .72), and statins (HR = .70). Additionally, GLP-1 RA use was protective against wet AMD but only when comparing patients taking insulin (HR = .62) and statins (HR = .69).[32]

Shor et al used a nationwide Canadian EHR database to compare 46,334 patients taking GLP-1 RAs with 92,668 controls over a follow-up period of 6 months to 3 years.[33] They found that the HR for developing wet AMD was 2.21 in GLP-1 RA users compared with controls. However, this study had limited duration of drug use and a lack of controls in the regression model for wet AMD risk factors, such as baseline PDR and DME status, smoking history, hemoglobin A1c, and history of dry AMD. Additional research with rigorous study design is needed to clarify these relationships.

## IIH

Several studies have explored the effect of GLP-1 RA use on IIH. A phase 2 trial studied exenatide usage on intracranial pressure (ICP) in patients with IIH over 12 weeks.[34] In the double-blind study, seven patients received subcutaneous exenatide twice daily and eight patients received placebo. By the end of the study, the ICP in exenatide users decreased by 5.6 ± 3.0 cmCSF compared with controls ($P$ = .058).

Another study investigated the effect of GLP-1 RAs on IIH symptoms, such as monthly headache days and visual outcomes.[35] While visual parameters such as field defects and visual acuity were not significantly different between groups, GLP-1 RA users (n = 7) reported fewer daily headaches ($P$ = .02) compared with controls (n = 8). While these results are promising, the sample sizes are very small, and further studies are warranted to support these findings.

## NAION

The effect of GLP-1 RAs on NAION is inconsistent across studies. In a retrospective cohort study of 16,827 patients in a single-center neuroophthalmology clinic, Hathaway et al found that semaglutide use was significantly associated with an increased incidence of NAION among patients with diabetes (HR = 4.28).[36] The risk was further elevated in patients without diabetes taking semaglutide for weight loss (HR = 7.64, $P < .001$). These results may have limited generalizability due to bias introduced by the study's design, including the treatment setting (ie, a neuroophthalmology clinic) and potential worse baseline health in patients taking semaglutide compared with matched controls.[37]

Several studies using large databases have attempted to replicate these results. Simonsen et al used the Norwegian and Danish national health registries and found an increased risk of NAION development with semaglutide initiation (HR = 2.81).[38] Grauslund et al identified all patients with diabetes in Denmark's national health registry and found that semaglutide was an independent predictor of incident NAION (HR = 2.19).[39] However, this study did not control for relevant risk factors such as smoking, blood pressure, and body mass index. Hsu et al used the TriNetX platform to study the association between semaglutide use and the incidence of NAION and found that it was associated with an increased risk in patients with diabetes at the 2-, 3-, and 4-year timepoints but not within 1 year of GLP-1 RA initiation.[40] Due to the deidentified nature of these databases, however, none of these large-scale cohort studies could account for treatment adherence and duration of exposure, and they lacked access to ophthalmic examination data.[41]

Additionally, in retrospective cohort analyses also using the TriNetX database, both Chou et al and Abbass et al found no association between semaglutide use and risk of NAION.[42,43] Of note, Abbass et al did not control for hemoglobin A1c, lipid levels, or history of cataract surgery, which could introduce bias.[44,45] Using the FDA Sentinel System, Maro et al found that the incidence of NAION was not increased within 6 months of semaglutide initiation.[46] Finally, Klonoff et al, using the Arcadia patient registry, also found no significant increase in NAION risk in patients taking semaglutide.[47] In June 2025, the European Medicines Agency recommended cessation of semaglutide use if a patient is newly diagnosed with NAION. However, the AAO and the North American Neuro-Ophthalmology Society do not support this blanket recommendation. Instead, they advise patients who develop NAION to engage in shared decision making with their providers about whether to discontinue the drug based on individual risks. Their reasoning includes the potentially significant systemic side effects of stopping semaglutide and the lack of evidence for a causative link between GLP-1 RAs and NAION.[48]

## MORE INFORMATION IS NEEDED

The newfound potential effects of GLP-1 RAs across numerous ophthalmic diseases have sparked excitement, concern, and confusion among ophthalmologists and patients alike. Many of these studies are from large databases, which are powerful tools in elucidating patterns on a population level, but can also be misleading due to their immense statistical power. They could produce findings that may be due to the bias inherent in retrospective studies. For example, ICD diagnosis codes for ophthalmic diseases can be unreliable and inaccurate,[49,50] particularly in national datasets in which manual validation of data is not possible.

Consequently, caution should be exercised when interpreting findings from large EHR studies. Future large database studies should provide increased methodologic transparency to support reproducible results.[51] Additionally, studies incorporating imaging data, visual function data, and prospective trials are warranted to further characterize the true effect of GLP-1 RA use on ocular diseases. ■


1. Shah M, Vella A. Effects of GLP-1 on appetite and weight. *Rev Endocr Metab Disord*. 2014;15(3):181-187.
2. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002.
3. Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. *Ther Adv Endocrinol Metab*. 2015;6(1):19-28.
4. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662.
5. Yusta B, Baggio LL, Estall JL, et al. GLP-1 receptor activation improves beta cell function and survival following induction of endoplasmic reticulum stress. *Cell Metab*. 2006;4(5):391-406.
6. van Bloemendaal L, Veltman DJ, Ten Kulve JS, et al. Brain reward-system activation in response to anticipation and consumption of palatable food is altered by glucagon-like peptide-1 receptor activation in humans. *Diabetes Obes Metab*. 2015;17(9):878-886.
7. Alharbi SH. Anti-inflammatory role of glucagon-like peptide 1 receptor agonists and its clinical implications. *Ther Adv Endocrinol Metab*. 2024;15:20420188231222367.
8. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131-2157.
9. Oezer K, Kolibabka M, Gassenhuber J, et al. The effect of GLP-1 receptor agonist lixisenatide on experimental diabetic retinopathy. *Acta Diabetol*. 2023;60(11):1551-1565.
10. Ramos H, Bogdanov P, Sampedro J, Huerta J, Simó R, Hernández C. Beneficial effects of glucagon-like peptide-1 (GLP-1) in diabetes-induced retinal abnormalities: involvement of oxidative stress. *Antioxidants (Basel)*. 2020;9(9):846.
11. Wei L, Mo W, Lan S, et al. GLP-1 RA improves diabetic retinopathy by protecting the blood-retinal barrier through GLP-1R-ROCK-p-MLC signaling pathway. *J Diabetes Res*. 2022;2022:1861940.
12. Müller TD, Finan B, Bloom SR, et al. Glucagon-like peptide 1 (GLP-1). *Mol Metab*. 2019;30:72-130.
13. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *New Engl J Med*. 2016;375(19):1834-1844.
14. Vilsbøll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes Obes Metab*. 2018;20(4):889-897.
15. Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA1c change and diabetic retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: a meta-analysis and meta-regression. *Diabetes Care*. 2021;44(1):290-296.
16. Kapoor I, Sarvepalli SM, D'Alessio D, Grewal DS, Hadziahmetovic M. GLP-1 receptor agonists and diabetic retinopathy: A meta-analysis of randomized clinical trials. *Surv Ophthalmol*. 2023;68(6):1071-1083.
17. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *New Engl J Med*. 2019;381(9):841-851.
18. Wai KM, Mishra K, Koo E, et al. Impact of GLP-1 agonists and SGLT-2 inhibitors on diabetic retinopathy progression: an aggregated electronic health record data study. *Am J Ophthalmol*. 2024;265:39-47.
19. Lin TY, Kang EYC, Shao SC, et al. Risk of diabetic retinopathy between sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. *Diabetes Metab J*. 2023;47(3):394-404.
20. Ko J, Moon SI. Risk of diabetic retinopathy between sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists (Diabetes Metab J 2023;47:394-404). *Diabetes Metab J*. 2023;47(4):571-572.
21. Lum F. Comment on impact of GLP-1 agonists and SGLT-2 inhibitors on diabetic retinopathy progression: an aggregated electronic health record study. *Am J Ophthalmol*. 2024;268:416.
22. Zheng D, Li N, Hou R, et al. Glucagon-like peptide-1 receptor agonists and diabetic retinopathy: nationwide cohort and Mendelian randomization studies. *BMC Med*. 2023;21(1):40.
23. Joo JH, Sharma N, Shaia J, et al. The effect of glucagon-like peptide-1 receptor agonists on diabetic retinopathy at a tertiary care center. *Ophthalmol Sci*. 2024;4(6):100547.
24. Tauqeer Z, Bracha P, Hua P, Yu Y, Cui QN, VanderBeek BL. Glucagon-like peptide-1 receptor agonists are not associated with an increased risk of progressing to vision-threatening diabetic retinopathy. *Ophthalmic Epidemiol*. 2025;32(4):390-393.
25. Ueda P, Pasternak B, Eliasson B, et al. Glucagon-like peptide 1 receptor agonists and risk of diabetic retinopathy complications: cohort study in nationwide registers from two countries. *Diabetes Care*. 2019;42(6):e92-e94.
26. Long-term effects of semaglutide on diabetic retinopathy in subjects with type 2 diabetes. Accessed June 21, 2025. clinicaltrials.gov/study/NCT03811561
27. Muayad J, Loya A, Hussain ZS, et al. Comparative effects of glucagon-like peptide 1 receptor agonists and metformin on glaucoma risk in patients with type 2 diabetes. *Ophthalmology*. 2025;132(3):271-279.

28. Niazi S, Gnesin F, Thein AS, et al. Association between glucagon-like peptide-1 receptor agonists and the risk of glaucoma in individuals with type 2 diabetes. *Ophthalmology*. 2024;131(9):1056-1063.
29. Eng K, Zebardast N, Boland MV, et al. Sodium-glucose cotransporter 2 inhibitors for the primary prevention of glaucoma in patients with type 2 diabetes: a target trial emulation. *Am J Ophthalmol*. 2025;271:286-298.
30. Amaral DC, Guedes J, Cruz MRB, et al. GLP-1 receptor agonists use and incidence of glaucoma: a systematic review and meta-analysis. *Am J Ophthalmol*. 2025;271:488-497.
31. Lawrence ECN, Guo M, Schwartz TD, et al. Topical and systemic GLP-1R agonist administration both rescue retinal ganglion cells in hypertensive glaucoma. *Front Cell Neurosci*. 2023;17:1156829.
32. Allan KC, Joo JH, Kim S, et al. Glucagon-like peptide-1 receptor agonist impact on chronic ocular disease including age-related macular degeneration. *Ophthalmology*. 2025;132(7):748-757.
33. Shor R, Mihalache A, Noori A, et al. Glucagon-like peptide-1 receptor agonists and risk of neovascular age-related macular degeneration [published online ahead of print June 5, 2025]. *JAMA Ophthalmol*.
34. Mitchell JL, Lyons HS, Walker JK, et al. The effect of GLP-1RA exenatide on idiopathic intracranial hypertension: a randomized clinical trial. *Brain*. 2023;146(5):1821-1830.
35. Krajnc N, Itariu B, Macher S, et al. Treatment with GLP-1 receptor agonists is associated with significant weight loss and favorable headache outcomes in idiopathic intracranial hypertension. *J Headache Pain*. 2023;24(1):89.
36. Hathaway JT, Shah MP, Hathaway DB, et al. Risk of nonarteritic anterior ischemic optic neuropathy in patients prescribed semaglutide. *JAMA Ophthalmol*. 2024;142(8):732-739.
37. Amini A, Hamann S, Larsen M. Semaglutide and non-arteritic anterior ischaemic optic neuropathy: Review and interpretation of reported association [published online ahead of print March 8, 2025]. *Acta Ophthalmol*.
38. Simonsen E, Lund LC, Ernst MT, et al. Use of semaglutide and risk of non-arteritic anterior ischemic optic neuropathy: A Danish-Norwegian cohort study. *Diabetes Obes Metab*. 2025;27(6):3094-3103.
39. Grauslund J, Taha AA, Molander LD, et al. Once-weekly semaglutide doubles the five-year risk of nonarteritic anterior ischemic optic neuropathy in a Danish cohort of 424,152 persons with type 2 diabetes. *Int J Retina Vitreous*. 2024;10(1):97.
40. Hsu AY, Kuo HT, Wang YH, et al. Semaglutide and nonarteritic anterior ischemic optic neuropathy risk among patients with diabetes. *JAMA Ophthalmol*. 2025;143(5):400-407.
41. Malerbi FK, Bertoluci MC. Semaglutide, type 2 diabetes, and the risk of nonarteritic anterior ischemic optic neuropathy. *International Journal of Retina and Vitreous*. 2025;11(1):8.
42. Chou CC, Pan SY, Sheen YJ, et al. Association between semaglutide and Nonarteritic anterior ischemic optic neuropathy: a multinational population-based study. *Ophthalmology*. 2025;132(4):381-388.
43. Abbass NJ, Nahlawi R, Shaia JK, et al. The effect of semaglutide and GLP-1 RAs on risk of nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol*. 2025;274:24-31.
44. Abbass NJ, Allan KC, Talcott KE, Singh RP. Reply to comment on the effect of semaglutide and GLP-1 RAs on risk of nonarteritic anterior ischemic optic neuropathy [published online ahead of print June 20, 2025]. *Am J Ophthalmol*.
45. Hsu AY, Lin CJ, Shao YC, Tsai YY, Wang YH, Wei JCC. Comment on: the effect of semaglutide and GLP-1 RAs on risk of nonarteritic anterior ischemic optic neuropathy [published online ahead of print June 20, 2025]. *Am J Ophthalmol*.
46. Maro JC, Platt R, Toh S. considerations regarding association of semaglutide and nonarteritic anterior ischemic optic neuropathy. *JAMA Ophthalmol*. 2024;142(12):1176.
47. Klonoff DC, Hui G, Gombar S. Real-world evidence assessment of the risk of nonarteritic anterior ischemic optic neuropathy in patients prescribed semaglutide. *J Diabetes Sci Technol*. 2024;18(6):1517-1518.
48. Should You Stop Taking GLP-1 Drugs Like Ozempic if You Experience Vision Loss? Nation's Ophthalmologists Respond to European Agency's New Recommendation. AAO. July 7, 2025. Accessed July 15, 2025. bit.ly/3IHDEm6
49. Cai CX, Michalak SM, Stinnett SS, Muir KW, Fekrat S, Borkar DS. Effect of ICD-9 to ICD-10 transition on accuracy of codes for stage of diabetic retinopathy and related complications: results from the CODER Study. *Ophthalmol Retina*. 2021;5(4):374-380.
50. Chen JS, Copado IA, Vallejos C, et al. Variations in electronic health record-based definitions of diabetic retinopathy cohorts: a literature review and quantitative analysis. *Ophthalmol Sci*. 2024;4(4):100468.
51. Cai CX, Hribar M, Nishimura A. Conflicting results—need for more transparent and reproducible research. *JAMA Ophthalmol*. 2025;143(5):408-409.

**SURAJ BALA, BS**
- Medical Student, Hackensack Meridian School of Medicine, Nutley, New Jersey
- suraj.bala@richmond.edu
- Financial disclosure: None

**JULIA H. JOO, MD**
- PGY-1 Ophthalmology Resident, Cole Eye Institute, Cleveland Clinic, Cleveland
- JOOJ5@ccf.org
- Financial disclosure: None

**ALEKSANDRA V. RACHITSKAYA, MD**
- Vitreoretinal Surgery Physician, Cole Eye Institute, Cleveland Clinic, Cleveland
- Associate Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine, Cleveland
- Editorial Advisory Board Member, *Retina Today*
- rachita@ccf.org
- Financial disclosure: Consultant (4DMT, Abbvie, Alcon, Apellis, Astellas, Boehringer Ingelheim, Carl Zeiss Meditec, EyePoint, Genentech/Roche, Ocular Therapeutix, Regeneron, Samsara); Scientific Advisory Board (Samsara); Speakers' Bureau (Apellis, Astellas, Genentech/Roche), Regeneron); Research Grants (Apellis, Beacon Therapeutics, DRCR Retina Network, Genentech/Roche, Regeneron)

*(Continued from page 21)*

motion artifacts. Improved optics and pupil tracking may allow imaging closer to the ora serrata without extreme gaze. Emerging AI tools could automate detection and quantification of peripheral pathology and streamline interpretation with objective metrics. ■

1. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254(5035):1178-1181.
2. Choma M, Sarunic M, Yang C, Izatt J. Sensitivity advantage of swept source and Fourier domain optical coherence tomography. *Opt Express*. 2003;11(18):2183-2189.
3. Klein T, Wieser W, Reznicek L, Neubauer A, Kampik A, Huber R. Multi-MHz retinal OCT. *Biomed Opt Express*. 2013;4(10):1890-1908.
4. Choudhry N, Duker JS, Freund KB, et al. Classification and guidelines for widefield imaging: recommendations from the International Widefield Imaging Study Group. *Ophthalmol Retina*. 2019;3(10):843-849.
5. Stanga PE, Pastor-Idoate S, Reinstein U, et al. Navigated single-capture 3D and cross-sectional wide-field OCT of the mid and peripheral retina and vitreoretinal interface. *Eur J Ophthalmol*. 2022;32(3):1642-1651.
6. Kovacs KD, Mahrous MA, Gonzalez L, et al. Feasibility and clinical utility of ultra-widefield-navigated swept-source optical coherence tomography imaging. *J Vitreoretin Dis*. 2021;5(5):396-404.
7. Eibenberger K, Sacu S, Rezar-Dreindl S, Pöcksteiner J, Georgopoulos M, Schmidt-Erfurth U. Monitoring retinoschisis and non-acute retinal detachment by optical coherence tomography: morphologic aspects and clinical impact. *Acta Ophthalmol*. 2017;95(7):710-716.
8. McNabb RP, Grewal DS, Mehta R, et al. Wide field of view swept-source optical coherence tomography for peripheral retinal disease. *Br J Ophthalmol*. 2016;100(10):1377-1382.
9. Yeoh J, Rahman W, Chen FK, da Cruz L. Use of spectral-domain optical coherence tomography to differentiate acquired retinoschisis from retinal detachment in difficult cases. *Retina*. 2012;32(8):1574-1580.
10. Stehouwer M, Tan SH, van Leeuwen TG, Verbraak FD. Senile retinoschisis versus retinal detachment, the additional value of peripheral retinal OCT scans (SL SCAN-1, Topcon). *Acta Ophthalmol*. 2014;92(3):221-227.
11. Rachitskaya AV, Yuan A, Singh RP, Sears JE, Schachat AP. Optical coherence tomography of outer retinal holes in senile retinoschisis and schisis-detachment. *Br J Ophthalmol*. 2017;101(4):445-448.
12. Lee WW, Muni RH. Single-capture ultra-widefield guided swept-source optical coherence tomography in the management of rhegmatogenous retinal detachment and associated peripheral vitreoretinal pathology. *Br J Ophthalmol*. 2023;107(9):1356-1362.
13. Witmer MT, Kozbial A, Daniel S, Kiss S. Peripheral autofluorescence findings in age-related macular degeneration. *Acta Ophthalmol*. 2012;90(6):e428-e433.
14. Zicarelli F, Preziosa C, Staurenghi G, Pellegrini M. Peripheral exudative haemorrhagic chorioretinopathy: a widefield imaging study. *Br J Ophthalmol*. 2021;105(10):1410-1414.
15. Gawęcki M, Kiciński K, Kucharczuk J, Teper S, Hubert M, Kuc T. Ultra-wide-field OCT measurements in patients with age-related macular degeneration in relation to their visual function. *Diagnostics*. 2024;14(24):2868.
16. Sodhi SK, Golding J, Trimboli C, Choudhry N. Feasibility of peripheral OCT imaging using a novel integrated SLO ultra-widefield imaging swept-source OCT device. *Int Ophthalmol*. 2021;41(8):2805-2815.
17. Xuan Y, Chang Q, Zhang Y, et al. Clinical observation of choroidal osteoma using swept-source optical coherence tomography and optical coherence tomography angiography. *Applied Sciences*. 2022;12(9):4472.
18. Saito R, Shinohara K, Tanaka N, Takahashi H, Yoshida T, Ohno-Matsui K. Association between dome-shaped macula and posterior staphyloma in highly myopic eyes investigated by ultra-widefield optical coherence tomography. *Retina*. 2021;41(3):646-652.
19. Nakao N, Igarashi-Yokoi T, Takahashi H, Xie S, Shinohara K, Ohno-Matsui K. Quantitative evaluations of posterior staphylomas in highly myopic eyes by ultra-widefield optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2022;63(8):20.
20. Zhao Q, Zhao X, Luo Y, Yang Z. Ultra-wide-field optical coherence tomography and gaussian curvature to assess macular and paravascular retinoschisis in high myopia. *Am J Ophthalmol*. 2024;263:70-80.
21. Nguyen TP, Ni S, Khan S, et al. Advantages of widefield optical coherence tomography in the diagnosis of retinopathy of prematurity. *Front Pediatr*. 2021;9:797684.
22. Skalet AH, Campbell JP, Jian Y. Ultrawide-field OCT for retinoblastoma. *Ophthalmology*. 2022;129(6):718.
23. Gaillard MC, Houghton S, Stathopoulos C, Munier FL. OCT-guided management of subclinical recurrent retinoblastoma. *Ophthalmic Genet*. 2018;39(3):338-343.

**SZILÁRD KISS, MD, FASRS**
- The Bob and Dolores Hope - Robert M. Ellsworth, MD, Distinguished Professor of Ophthalmology and Professor of Ophthalmology in Genetic Medicine, Weill Cornell Medical College, New York Presbyterian Hospital, New York, New York
- Editorial Advisory Board Member, *Retina Today*
- szk7001@med.cornell.edu
- Financial disclosure: Advisory Board (Regeneron); Consultant (Optos, Regeneron); Board of Directors (Adverum)

**PEYMAN RAZAVI, MD**
- Ophthalmology Resident, Weill Cornell Medical College, New York Presbyterian Hospital, New York, New York
- per4001@nyp.org
- Financial disclosure: None

# THE EMERGING ROLE OF AI IN DR SCREENING

## AI-powered technologies could help ophthalmologists meet the growing needs of this patient population.

By Jorge C. P. Rocha, MD, PhD, and Majda Hadziahmetovic, MD

Diabetes is a growing global health problem that affects nearly one in 10 adults worldwide. Projections suggest that, by 2045, the number of individuals living with diabetes will approach one billion globally.[1] In a 2021 report, the disease showed a higher prevalence in urban settings compared with rural areas (12.1% vs 8.3%, respectively) and in high-income compared with low-income countries (11.1% vs 5.5%, respectively).[1] However, future trends indicate a significant shift, with middle income countries expected to experience the most significant increase in diabetes prevalence.[1] The widespread and ever-evolving nature of diabetes, which exceeds geographic and socioeconomic expectations, underscores its complexity and global impact.

### GLOBAL TRENDS IN DR

Diabetic retinopathy (DR) remains a significant global public health challenge and a leading cause of vision loss among working-age adults.[2] DR is a progressive

### AT A GLANCE

- Although appropriate treatment can reduce the risk of vision loss by up to 90%, more than half of individuals with diabetic retinopathy (DR) remain undiagnosed, emphasizing the urgent need for improved screening, surveillance, and care delivery models.
- AI-powered technologies such as convolutional neural networks have led to major breakthroughs in image recognition with powerful applications in detecting DR.
- To address critical gaps in DR screening, we must shift toward a proactive strategy and create a dedicated task force composed of key stakeholders, including clinicians, policymakers, algorithm developers, payers, and patient advocates.

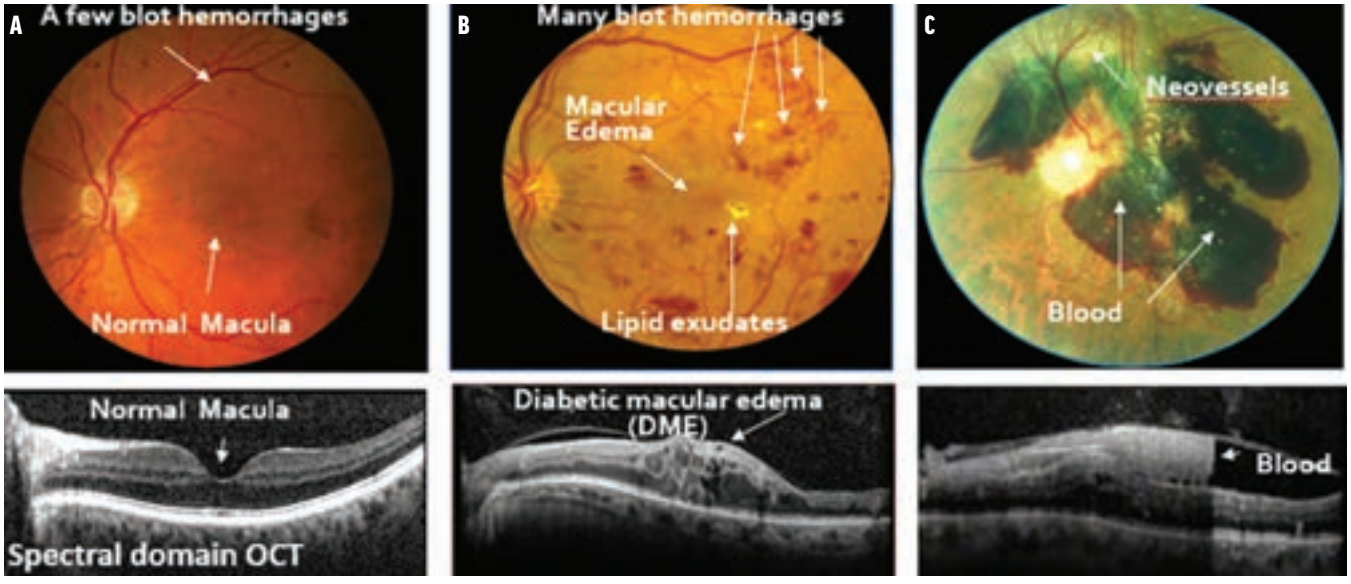



Figure. Many AI-powered screening tools can detect various stages of DR, including mild NPDR (A), moderate-to-severe NPDR (B), and PDR (C).

microvascular disease of the retina caused by long-standing, poorly controlled diabetes. Its clinical spectrum ranges from nonproliferative DR (NPDR) to proliferative (PDR), which is associated with complications such as vitreous hemorrhage and tractional retinal detachment. Diabetic macular edema can further compromise central vision in this patient population.

More than 75% of individuals living with diabetes for more than 2 decades will experience some form of DR.[3] The condition accounts for 4.8% of cases of blindness worldwide.[4]

Roughly one in four patients with any stage of DR will require intervention at some point. Although appropriate treatment can reduce the risk of vision loss by up to 90%, more than half of individuals with DR remain undiagnosed, emphasizing the urgent need for improved screening, surveillance, and care delivery models.[5-7] Despite this knowledge, screening rates are trending downward; in 2020, only 58.3% of adults diagnosed with diabetes had an eye examination within the last year, which is significantly lower than the year before (64.8%). Furthermore, only about 40% of patients at high risk of vision loss from DR receive timely and appropriate treatment; however, with proper disease management and timely intervention, DR can often be effectively controlled, significantly preserving vision.[8]

## SCREENING INITIATIVES

Faced with multiple comorbidities, individuals with diabetes are often forced to prioritize medical appointments, understandably placing general medicine and chronic disease management ahead of ophthalmic care. Additionally, limited access to specialized services in underserved regions and an insufficient ophthalmic workforce (a gap expected to widen in the coming years[9]) further restrict recommended DR surveillance. While numerous screening programs for DR have been proposed and piloted to emphasize early detection and prevention, only a few have demonstrated long-term sustainability.[10]

### Barriers to Adoption

Several barriers impede the widespread adoption of DR screening. These include the infrastructure challenges previously mentioned, particularly in rural and resource-limited settings, as well as difficulties in integrating DR screening programs into existing clinical workflows. Inconsistent reimbursement models and regulatory policies further complicate implementation. Moreover, reliance on asynchronous, "human-in-the-loop" interpretation (ie, the need for human interaction or intervention[11]) can introduce delays in communication and disrupt continuity of care.

A broader obstacle remains the lack of a unified community consensus on critical components, including optimal imaging modalities, the extent of retinal visualization (eg, widefield vs standard views), standardized grading rubrics, financial models, reimbursement structures, liability considerations, and data ownership. These challenges underscore the pressing need for a dedicated task force responsible for aligning stakeholders, defining best practices, and driving the strategic advancement of this long-overdue effort.

### AI-Powered DR Screening

Advances in machine learning have significantly affected the field of medicine, particularly ophthalmology. Machine learning has advanced even further with deep learning, which uses multi-layered neural networks with convoluted deductions similar to how the human brain works. AI technologies such as convolutional neural networks have led to

major breakthroughs in image recognition with powerful applications in detecting DR.

Training an AI screening algorithm for DR involves three key phases: learning, validating, and testing. In the initial learning phase, the algorithm is trained on carefully labeled retinal images, allowing it to self-adjust and recognize disease features. During validation, the algorithm is tested on a separate labeled dataset to fine-tune performance and ensure it generalizes the knowledge, rather than simply memorizing patterns. Finally, in the testing phase, the model is applied to large diverse populations (ideally using independent datasets) to confirm its accuracy and robustness across real-world clinical settings.[8,12]

Multiple well-established and emerging companies are competing to provide accurate, efficient, and accessible point-of-care screening solutions. In these settings, retinal images (typically color fundus photographs) are captured by nonexpert personnel and uploaded to the cloud, where proprietary AI algorithms perform automated interpretation. These sophisticated systems can generate diagnostic reports in less than 30 seconds, seamlessly integrating the results into electronic health records.

Moreover, the reports generated by AI-powered systems can go beyond simple binary identification (ie, DR presence or absence) and offer basic disease classification, distinguishing between early and more advanced changes and allowing for triage to the appropriate subspecialty eye care (Figure). Timely feedback of results directly to the ordering provider can enable immediate communication with patients, facilitate prompt referrals, reinforce the importance of follow-up care, and significantly improve patient adherence and engagement in disease management. This model stands in contrast to traditional physician-guided screening, where asynchronous image grading can result in substantial delays, thus disturbing continuity of care.[7]

## DIABETIC EYE DISEASE SCREENING IN BRAZIL

With strong support from our industry partners, we are launching a new initiative to screen for diabetic retinopathy in Brazil, the first of its kind to achieve large-scale patient capture while generating detailed insights across the entire implementation process. This effort will not only address the practical logistics of setting up and executing a nationwide screening program, but will also create one of the largest and most comprehensive diabetic retinopathy datasets in the region. We are hopeful that the framework established through this initiative will empower the broader ophthalmic and public health communities to advance this critically important mission to improve access, early detection, and outcomes for patients at risk of vision loss.

### Commercially Available AI-Powered DR Screening Systems

In 2018, LumineticsCore (formerly IDx-DR; Digital Diagnostics) became the first fully autonomous AI system in any field of medicine to receive FDA clearance through a de novo approval process. There are now three additional systems cleared by the FDA: EyeArt (Eyenuk), Aeye Diagnostic Screening (Aeye Health), and Retina-AI Galaxy (Retina-AI Health). Importantly, the 2021 introduction of CPT code 92229 made AI-supported DR screening reimbursement possible, promoting broader acceptance in the United States.

### CALL TO ACTION

Despite decades of research and established guidelines, DR screening continues to be underused, resulting in delayed diagnoses, preventable vision loss, and billions of dollars in health care costs for late-stage interventions that often yield suboptimal clinical outcomes. To address critical gaps, we must shift toward a proactive strategy and create a dedicated task force composed of key stakeholders, including clinicians, policymakers, developers, payers, and patient advocates. This broad collaboration is essential to define safe deployment, ensure thorough validation, and, ultimately, develop a unified, evidence-based screening protocol. ■

1. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119. Erratum in: *Diabetes Res Clin Pract*. 2023;204:110945.
2. Bourne RRA, Jonas JB, Bron AM, et al. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe in 2015: magnitude, temporal trends and projections. *Br J Ophthalmol*. 2018;102(5):575-585.
3. Upadhayay P, Singh N, Pandey M, et al. Unveiling the link between lifestyle risk factors and diabetic retinopathy. *Int J Diabetes Dev Ctries*. 2025;45:63-68.
4. World Health Organization. Prevention of blindness from diabetes mellitus: report of a WHO consultation in Geneva, Switzerland. World Health Organization. 2005. Accessed June 30, 2025. apps.who.int/iris/bitstream/handle/10665/43576/9241547123_eng.pdf
5. Lee PP, Feldman ZW, Ostermann J, Brown DS, Sloan FA. Longitudinal rates of annual eye examinations of persons with diabetes and chronic eye diseases. *Ophthalmology*. 2003;110(10):1952-1959.
6. Paz SH, Varma R, Klein R, Wu J, Azen SP. Los Angeles Latino eye study group: noncompliance with vision care guidelines in Latinos with type 2 diabetes mellitus: the Los Angeles Latino Eye Study. *Ophthalmology*. 2006;113(8):1372-1377.
7. Prevention and Health Promotion. Increase the proportion of adults with diabetes who have a yearly eye exam. US Department of Health and Human Services. Accessed June 20, 2025. health.gov/healthypeople/objectives-and-data/browse-objectives/diabetes/increase-proportion-adults-diabetes-who-have-yearly-eye-exam-d-04
8. Office of Disease Prevention and Health Promotion. Increase the proportion of adults with diabetes who have a yearly eye exam. US Department of Health and Human Services. Accessed June 30, 2025. health.gov/healthypeople/objectives-and-data/browse-objectives/diabetes/increase-proportion-adults-diabetes-who-have-yearly-eye-exam-d-04
9. Berkowitz ST, Finn AP, Parikh R, Kuriyan AE, Patel S. Ophthalmology workforce projections in the United States, 2020 to 2035. *Ophthalmology*. 2024;131(2):133-139.
10. Abou Taha A, Dinesen S, Vergmann AS, Grauslund J. Present and future screening programs for diabetic retinopathy: a narrative review. *Int J Retina Vitreous*. 2024;10(1):14.
11. Meng X-L. Data science and engineering with human in the loop, behind the loop, and above the loop. *Harvard Data Sci Rev*. 2023;5(2).
12. Dow ER, Chen KM, Zhao CS, et al. Artificial intelligence improves patient follow-up in diabetic retinopathy screening program. *Clinical Ophthalmol*. 2023;17:3323-3330.

**JORGE C. P. ROCHA, MD, PHD**
- Director and President, iRetina Eye Institute, Salvador, Bahia, Brazil
- jrocha1308@gmail.com
- Financial disclosure: None

**MAJDA HADZIAHMETOVIC, MD**
- Associate Professor of Ophthalmology, Department of Ophthalmology, Duke University Medical Center, Durham, North Carolina
- Associate Professor of Electrical and Computer Engineering, Pratt School of Engineering, Duke University, Durham, North Carolina
- majda.hadziahmetovic@duke.edu
- Financial disclosure: None

# Delivering Innovations for Subretinal Injections

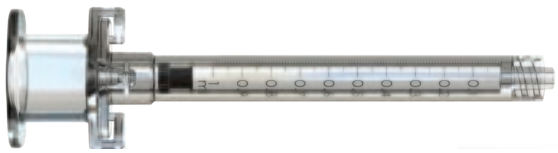
## New Silicone-Free MicroDose™ SF Injection Kit

Our MicroDose™ products set the standard for reliability and control during high precision subretinal injections. With the launch of our new MicroDose™ SF, we have added critical features such as a silicone-free syringe, removable plunger rod and dead-space reduction stopper. Combine either MicroDose™ device with one of our market leading specialized cannulas and create the ideal system for your surgical needs.

**Contact us today to find out more!**

NEW!


3315 MicroDose™ SF Injection Kit



3275 MicroDose™ Injection Kit

*Features*

| | | |
|---|---|---|
| ● | US FDA cleared for low-volume subretinal injections | ● |
| ● | Precise, pneumatically controlled injection using Alcon, DORC, or B+L vitrectomy consoles | ● |
| ● | 1mL syringe ideal for low-volume injection | ● |
| ● | Luer lock syringe allows for a wide variety of subretinal cannula options | ● |
| ● | Syringe can be pneumatically filled | ● |
| ● | Syringe can be manually filled utilizing the removable plunger rod | |
| ● | Silicone-free syringe eliminates risk of silicone droplets during injection | |
| ● | Unique stopper design reduces dead-space to approximately 10 microliters | |

MedOne®
www.medone.com

# UTILITY OF FLUORESCEIN ANGIOGRAPHY IN DME

If you want to assess vessel leakage and peripheral pathology in diabetic eye disease, FA is still your best bet.

By Jason Keil, MD, PhD; Caitlyn Cooper, MA; and Yannis M. Paulus, MD



Diabetic retinopathy (DR) remains a major burden on the health care system and continues to be the leading cause of legal blindness in working-age adults.[1] This will continue to be an immense challenge for the field, given the prediction that 191 million people will have DR and 56 million people will have vision-threatening disease by 2030.[2] Vision loss in DR can be secondary to multiple processes, including vitreous hemorrhage, tractional retinal detachment, macular ischemia, disorganization of the inner retinal layers, and diabetic macular edema (DME). Because DME remains the most prevalent mechanism of decreased visual acuity in patients with diabetes,[3] effective diagnostics and treatment of DME is critical.

## IMAGING IN DME

DME is evaluated on clinical examination as well as multimodal imaging, such as OCT, OCT angiography (OCTA), fundus photography, and fluorescein angiography (FA). FA is now used less frequently due to the invasive nature of the test, increased time of acquisition, and potential dye reactions, alongside the proliferation and increasing sophistication of alternative imaging modalities

## AT A GLANCE

- Although fluorescein angiography (FA) is now used less frequently, it remains a valuable imaging modality for patients with diabetic macular edema.
- Quantitative leakage on ultra-widefield FA is strongly correlated with diabetic retinopathy severity score as well as risk of disease progression.
- OCT and the increasing use of OCT angiography will further augment the role of FA in retinal vascular diseases such as diabetic retinopathy.

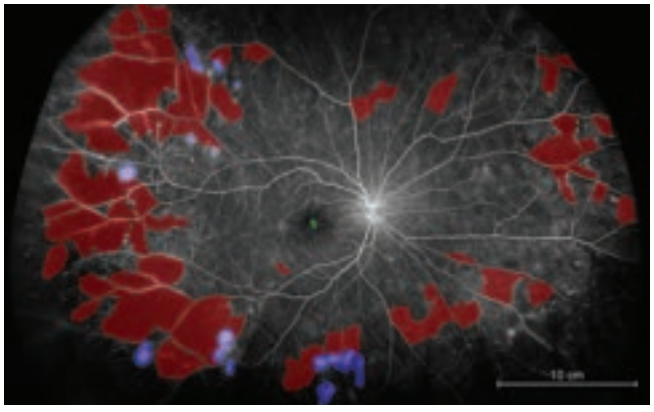


Figure 1. UWF FA of proliferative DR demonstrates areas of nonperfusion (red) and neovascularization (purple) and the foveal avascular zone (green). Following segmentation, biomarker areas can be calculated. Reproduced with permission from Fleifil S et al.[6]

such as OCTA, which can provide high-resolution vascular imaging to illuminate posterior pole vascular pathology. However, FA remains valuable as the only way to directly assess vessel leakage as well as to image retinal perfusion in the periphery. Thus, fluorescein images provide a functional correlate to the anatomic microstructural changes visualized on OCT and OCTA.

Ultra-widefield (UWF) imaging in conjunction with FA has demonstrated that peripheral retinal findings may aid in the identification of patients who will progress to more severe disease (Figure 1). Quantitative leakage on UWF FA is strongly correlated with DR severity score as well as risk of DR progression, including the transition from nonproliferative to proliferative disease.[4-7] Peripheral retinal findings also correlate with the presence of DME,[8-11] including quantitative areas of peripheral retinal nonperfusion, retinal vascular bed area, and the ischemic index. These measurements, all derived from FA images, could be potentially useful biomarkers to predict which patients may develop clinically significant DME. Notably, these studies have only used peripheral retinal data in their analysis, which suggests effects on the blood-retinal barrier in the posterior pole are either correlated with global VEGF levels or that peripheral retinal findings can be used as a proxy for pathologic transformation and breakdown of the blood-retinal barrier in the macula.

## THE MECHANICS OF FA

FA functions by imaging the location of the intravenous injected tracer molecule. The intravascular space is imaged, but perhaps more importantly, the efflux of this tracer out of the retinal intravascular space provides a direct measurement of blood-retinal barrier breakdown and leakage from microaneurysms or pathologic neovascular vessels. Direct visualization of leaking vessels that are driving the accumulation of cystic fluid also enables the possibility of precise targeting of focal laser to directly treat pathologic vessels.[12]

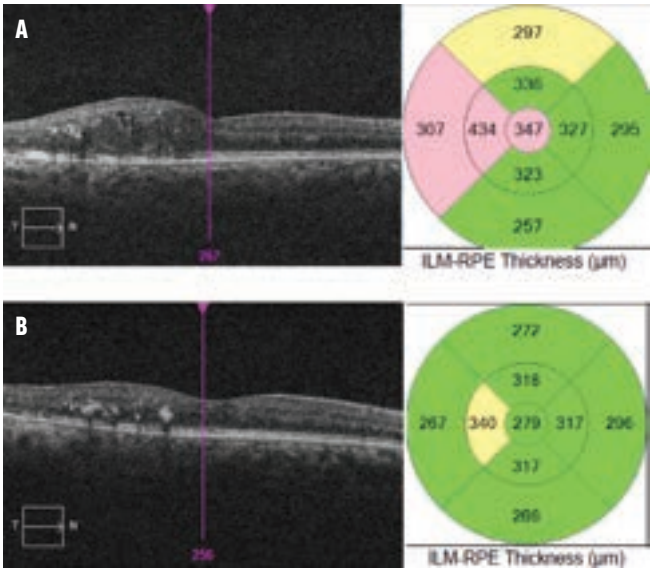



Figure 2. OCT of the macula and thickness measurement mapping before (A) and after (B) endpoint management laser therapy demonstrating a reduction in DME with fewer anti-VEGF injections. Reproduced with permission from Azzouz L et al.[15]

With appropriate protocols, FA can be treated in a quantitative fashion to define areas of nonperfusion, neovascular vessels, and total retinal blood vessels. Furthermore, the efflux of fluorescein dye from the intravascular space into the retina can be measured to quantify leakage. These are time-intensive processes for a clinician to perform, although future measurements are likely to be less dependent on human effort and oversight. Computational advances have recently led to the development of advanced image analysis software and AI algorithms that may lead to automated image interpretation and analysis.[13] This will be an important tool to increase throughput with retina specialist oversight or to potentially automate decision making.

## TREATMENT CONSIDERATIONS

Anti-VEGF therapy is often quite successful in resolving cystoid fluid with resultant improvement in visual acuity. However, anti-VEGF therapy is not a panacea for all patients with edema, as some demonstrate persistent disease activity despite therapy. In addition, treatment with an anti-VEGF agent is typically avoided in certain patients, such as those who are pregnant or who have certain medical conditions.

Some patients are resistant to multiple injections and multiple different anti-VEGF agents.[14] In cases where specific areas of leakage are suspected, focal laser remains a viable option for DME monotherapy or as an adjuvant therapy with anti-VEGF injections. Adjuvant focal laser therapy can decrease the number of required injections by 49% and increase the time between injections, effectively decreasing injection burden and endophthalmitis risk (Figure 2).[15] Laser is also an attractive option in situations

## FA REMAINS VALUABLE AS THE ONLY WAY TO DIRECTLY ASSESS VESSEL LEAKAGE AND IMAGE RETINAL PERFUSION IN THE PERIPHERY.

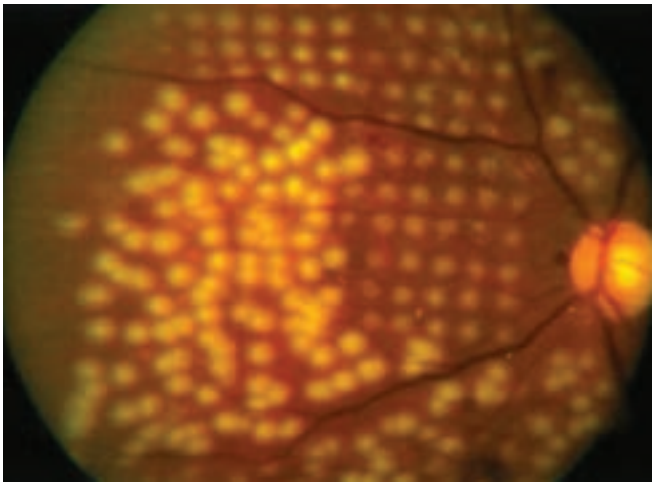


**Figure 3. When comparing conventional laser (lower left) with patterned scanning laser (upper right), note the more uniformly spaced, less intense small spots provided by pattern scanning laser therapy. Reproduced with permission from Paulus YM et al.[19]**

where intravitreal steroids or anti-VEGF therapy are contraindicated or unavailable. Development of novel laser therapies—such as selective retinal therapy, subthreshold diode micropulse laser, and endpoint management technology—continues to improve the safety of focal laser in ways that are less destructive than traditional photocoagulation (Figure 3).[16-19]

### FUTURE UTILITY

OCT and the increasing use of OCTA will further augment the role of FA in retinal vascular diseases and DR specifically. High-resolution vessel imaging can be obtained with OCTA,[20] with the potential to identify microaneurysms that anatomically occur in close proximity to areas of cystoid macular edema. While this is suggestive of pathologic blood-retinal barrier dysfunction, only FA can demonstrate leakage via extravascular extravasation of contrast.

These imaging modalities continue to complement each other, and we continue to value FA as an important imaging modality to help us treat patients with DR and DME. ■

1. Bourne RRA, Jonas JB, Bron AM, et al. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe in 2015: magnitude, temporal trends and projections. *Br J Ophthalmol*. 2018;102(5):575-585.
2. Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. *Clin Exp Ophthalmol*. 2016;44(4):260-277.
3. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis (Lond)*. 2015;2:17.
4. Ehlers JP, Josic K, Yordi S, et al. Assessment of baseline ultrawidefield fluorescein angiographic quantitative leakage parameters with ultrawidefield fundus features and clinical parameters in diabetic retinopathy in protocol AA. *Ophthalmol Retina*. 2025;9(3):243-252.
5. Iyengar RS, Fleifil S, Aaberg MT, et al. Quantitative ultra-widefield fluorescein angiography biomarkers in diabetic retinopathy and association with treatment and progression. *Clin Ophthalmol*. 2024;18:4019-4028.
6. Fleifil S, Azzouz L, Yu G, Powell C, Bommakanti N, Paulus YM. Quantitative biomarkers of diabetic retinopathy using ultra-widefield fluorescein angiography. *Clin Ophthalmol*. 2024;18:1961-1970.
7. Silva PS, Marcus DM, Liu D, et al. Association of ultra-widefield fluorescein angiography-identified retinal nonperfusion and the risk of diabetic retinopathy worsening over time. *JAMA Ophthalmol*. 2022;140(10):936-945.
8. Huang RS, Mihalache A, Popovic MM, et al. Quantitative fluorescein angiography biomarkers in diabetic macular edema. *Retina*. 2025;45(6):1125-1133.
9. Fan W, Wang K, Ghasemi Falavarjani K, et al. Distribution of nonperfusion area on ultra-widefield fluorescein angiography in eyes with diabetic macular edema: DAVE Study. *Am J Ophthalmol*. 2017;180:110-116.
10. Fan W, Uji A, Wang K, et al. Severity of diabetic macular edema correlates with retinal vascular bed area on ultra-wide field fluorescein angiography: DAVE Study. *Retina*. 2020;40(6):1029-1037.
11. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. *Br J Ophthalmol*. 2012;96(5):694-698.
12. Maltsev DS, Kulikov AN, Burnasheva MA, Kazak AA, Chhablani J. Efficacy of navigated focal laser photocoagulation in diabetic macular edema planned with en face optical coherence tomography versus fluorescein angiography. *Int Ophthalmol*. 2020;40(8):1913-1921.
13. Zhao PY, Bommakanti N, Yu G, Aaberg MT, Patel TP, Paulus YM. Deep learning for automated detection of neovascular leakage on ultra-widefield fluorescein angiography in diabetic retinopathy. *Sci Rep*. 2023;13(1):9165.
14. Bressler NM, Beaulieu WT, Glassman AR, et al. persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(3):257-269.
15. Azzouz L, Durrani A, Zhou Y, Paulus YM. Adjunct nondamaging focal laser reduces intravitreal injection burden in diabetic macular edema. *Photonics*. 2023;10(10):1165.
16. Everett LA, Paulus YM. Laser therapy in the treatment of diabetic retinopathy and diabetic macular edema. *Curr Diab Rep*. 2021;21(9):35.
17. Lois N, Campbell C, Waugh N, et al. Diabetic macular edema and diode subthreshold micropulse laser: a randomized double-masked noninferiority clinical trial. *Ophthalmology*. 2023;130(1):14-27.
18. Tai F, Nanji K, Garg A, et al. Subthreshold compared with threshold macular photocoagulation for diabetic macular edema: a systematic review and meta-analysis. *Ophthalmol Retina*. 2024;8(3):223-233.
19. Paulus YM, Palanker D, Blumenkranz MS. Short-pulse laser treatment: redefining retinal therapy. *Retinal Physician*. 2010;7(1):54-56.
20. Peres MB, Kato RT, Kniggendorf VF, et al. Comparison of optical coherence tomography angiography and fluorescein angiography for the identification of retinal vascular changes in eyes with diabetic macular edema. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(11):1013-1019.

**JASON KEIL, MD, PHD**
- Vitreoretinal Fellow, Wilmer Eye Institute, Department of Ophthalmology, Johns Hopkins University, Baltimore
- jmkeil22@gmail.com
- Financial disclosure: None

**CAITLYN COOPER, MA**
- Medical Student, Arizona College of Osteopathic Medicine, Midwestern University, Glendale, Arizona
- caitlyn.cooper@midwestern.edu
- Financial disclosure: None

**YANNIS M. PAULUS, MD**
- Jonas Friedenwald Professor, Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore
- Associate Professor, Department of Biomedical Engineering, Johns Hopkins University, Baltimore
- ypaulus1@jh.edu
- Financial disclosure: Consultant (Capvision, ClearView Healthcare Partners, Connected Research and Consulting, Deerfield Institute, Health Advances, Iridex, MediBeacon, Medspoke, Putnam Associated Consulting, Qessential Medical Market Research, TDG Health); Equity (PhotoSonoX)


When it comes to retinal health
Let's talk about
THE MITOCHONDRIA IN THE ROOM.
They have been there all along—powering the cells, sustaining retinal health.
And as they begin to fade, so does everything that depends on them.
Let's talk about mitochondrial health
Sponsored by
Stealth BIOTHERAPEUTICS

# MANAGING DR IN PATIENTS WITH GOOD VISION

## The DRCR Retina Network sheds light on the optimal treatment approaches.

By Gage Hazelton, BA, and Deepak Sambhara, MD


Anti-VEGF medications have transformed the treatment landscape for diabetic macular edema (DME). Approximately 90% of eligible eyes with DME receive anti-VEGF therapy, which is employed as the first-line treatment in nearly 80% of cases.[1] Thus, many studies have explored the most effective agents and the optimal treatment timing, particularly in patients presenting with good visual acuity (VA). Here, we examine the literature shaping how clinicians make informed decisions regarding the management of DME in patients with good baseline VA.

### CHOOSING THE RIGHT AGENT

In 2013, the Medicare reimbursement cost for a single intravitreal injection was approximately $1,950 for 2 mg aflibercept (Eylea, Regeneron), $1,200 for ranibizumab (Lucentis, Genentech/Roche), and $50 for bevacizumab (Avastin, Genentech/Roche).[2] This stark cost difference led the Diabetic Retinopathy Clinical Research (DRCR) Retina Network to investigate the efficacy and safety of these agents in Protocol T.[2]

### AT A GLANCE

- DRCR Retina Network's Protocol T demonstrated that, for patients with diabetic macular edema (DME) and good baseline visual acuity, 2 mg aflibercept (Eylea, Regeneron), ranibizumab (Lucentis, Genentech/Roche), and bevacizumab (Avastin, Genentech/Roche) were equally effective.
- Protocol V found no significant difference in visual acuity loss at 2 years for patients with DME treated with immediate anti-VEGF therapy, observation with deferred anti-VEGF therapy, or initial focal laser with deferred anti-VEGF therapy.
- Opting for initial observation or laser therapy over immediate anti-VEGF treatment could result in substantial long-term cost savings.

Patients were randomly assigned to receive aflibercept, bevacizumab, or ranibizumab.[2] At the 1-year mark, aflibercept showed superior vision improvement compared with the other agents, but only in patients with a baseline VA of 20/50 or worse. Among patients with a VA between 20/32 and 20/40, the differences between treatments were not statistically significant.[2]

At 2 years, the results were similar: No significant differences were observed among patients with an initial VA of 20/32 to 20/40. However, among those with a VA worse than 20/50, aflibercept showed a significant advantage over bevacizumab but not over ranibizumab (Figure).[3] Thus, Protocol T concluded that, for patients with good baseline VA, the three agents were equally effective. This provided clinicians with strong evidence to consider more cost-effective options, thereby reducing the financial burden on patients and the health care system. With this information, attention shifted to the next question: When should treatment begin for patients with good initial VA?

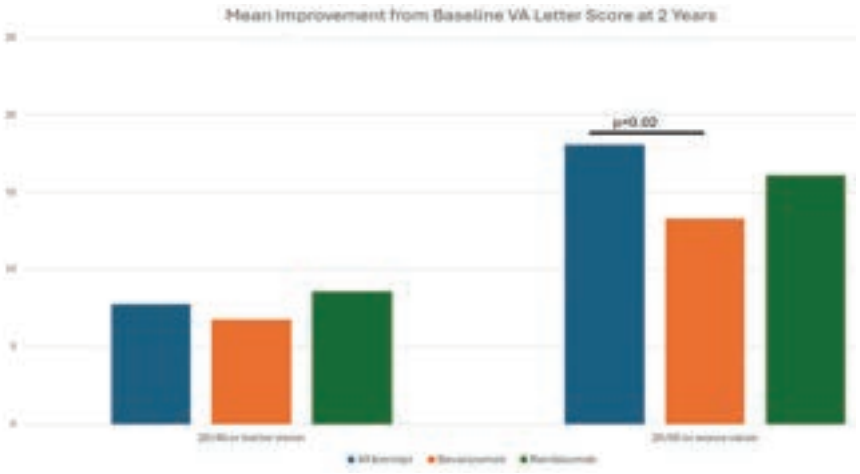



**Figure. In Protocol T, the mean improvement from baseline at 2 years was only statistically significant in patients with a baseline VA worse than 20/50 who were treated with bevacizumab compared with those treated with aflibercept.[3]**

DRCR Retina Network's Protocol V then compared the benefits of three treatment approaches: immediate anti-VEGF therapy, observation with anti-VEGF therapy if VA worsened, or initial focal laser with deferred anti-VEGF therapy.[4] Study patients had a baseline VA of 20/25 or better. The study found no significant difference in VA loss at 2 years—mean VA remained 20/20 across all groups.[4]

## DOES COST MATTER?

Based on these findings, researchers have noted the potential for significant cost implications with various treatment approaches.[5,6] One analysis took a deeper dive into these data to forecast cost savings from Protocol V.[6] The study reported that the per-person cost for the aflibercept group was $15,926 in 2019, $5,537 for the observation group, and $3,729 for the laser group. In the observation and laser groups, 80% and 64% of the costs, respectively, were associated with injection-related expenses due to worsening VA.[6]

The researchers subsequently conducted a 10-year population cost analysis to assess the economic effect of patients with center-involved DME and a VA of 20/25 or better undergoing the respective treatment options. The team found a total savings of $10.33 billion when starting with observation compared with initiating treatment with aflibercept and $11.35 billion when starting with laser therapy instead of aflibercept. Consequently, the authors concluded that, while individual circumstances may influence treatment decisions, opting for initial observation or laser therapy over immediate anti-VEGF treatment could result in substantial long-term cost savings.[6]

## RECENT SHIFTS

Since the completion of Protocol V, the proportion of patients with type 2 diabetes on glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has nearly doubled.[7] A large retrospective cohort study found that patients with diabetes (regardless of prior retinopathy) on monotherapy with GLP-1 RAs experienced significantly higher rates of new-onset DME at every follow-up interval and showed an increased risk of progression to proliferative diabetic retinopathy.[8] They also had a greater need for anti-VEGF therapy at 1 and 3 years after treatment initiation compared with patients receiving sodium-glucose co-transporter 2 inhibitor monotherapy.[8] Thus, patients on GLP-1 RAs may warrant closer observation and more in-depth discussions on when to initiate treatment for diabetic eye disease.

## NEWER TREATMENT OPTIONS

One major issue with anti-VEGF therapy is the burden it places on patients—an issue newer therapies aim to address. In the PHOTON trial of 8 mg aflibercept (Eylea HD, Regeneron) for DME, researchers compared 8 mg aflibercept every 12 or 16 weeks after three monthly loading doses versus 2 mg aflibercept every 8 weeks after five monthly loading doses.[9] They found that adverse event rates and improvements in BCVA and anatomic outcomes were comparable between the groups.[9] Patients with baseline VA of 20/40 or better and those with 20/50 or worse saw gains in BCVA, with the greatest improvement in the latter group. Among patients with baseline VA better than 20/40, more were able to maintain longer dosing intervals.[10] Therefore, in patients with DME and good baseline VA, 8 mg aflibercept may be a viable option to reduce treatment burden.

In the YOSEMITE trial of faricimab (Vabysmo, Genentech/Roche), researchers compared three regimens for DME: faricimab every 6 weeks, faricimab using a treat-and-extend protocol, and 2 mg aflibercept every 8 weeks. The study

**TABLE. SUMMARY OF STUDIES FOR TREATING DME**

| Protocol | Baseline VA | Treatment Arms | Summary of Findings |
|---|---|---|---|
| Protocol T | 20/32 to 20/320 | 2 mg aflibercept vs bevacizumab vs ranibizumab | No significant difference in treatment outcomes in patients with baseline VA of 20/32 to 20/40 |
| Protocol V | 20/25 or better | Immediate anti-VEGF vs observation with deferred anti-VEGF vs initial focal laser with deferred anti-VEGF | No significant difference in long-term outcomes |
| PHOTON | 20/50 or worse and 20/40 or better | 2 mg aflibercept vs 8 mg aflibercept | Reduced treatment burden with similar outcomes |
| YOSEMITE | 20/40 to 20/400 | Faricimab every 6 weeks, faricimab treat-and-extend vs aflibercept every 8 weeks | Reduced treatment burden w/ similar VA outcomes and greater CST reduction in faricimab groups compared with aflibercept |

included patients with baseline VA ranging from approximately 20/40 to 20/400.[11] At 2 years, improvements in BCVA were similar between groups. Notably, the treat-and-extend group achieved these results with an average of 10 injections versus 15 for the aflibercept group.[11] More faricimab-treated patients achieved central subfield thickness < 325 µm and absence of DME compared with the aflibercept group.[11] Although faricimab may be able to reduce treatment burden while maintaining efficacy, this trial did not include patients with a baseline BCVA better than 20/40.

In 2023, a smaller retrospective study assessed DME patients who were refractory to aflibercept and ranibizumab who were switched to a prn faricimab protocol. With a mean baseline VA of 20/40, these patients were able to extend their treatment intervals.[12] However, the study's small sample size and short follow-up limit its generalizability.[12]

New real-world data showed that among patients starting faricimab, 50% had VA of 20/40 or better. Moreover, injection frequency decreased 6 months after switching, indicating extended treatment intervals.[13] This supports the potential benefit of faricimab in DME patients with good baseline VA. Importantly, most eyes in these studies were previously treated with another anti-VEGF agent, so further research is needed to evaluate faricimab as initial therapy in treatment-naïve patients with good baseline VA.

## PUTTING IT ALL TOGETHER

Deciding how to manage patients presenting with good VA is multifactorial and warrants individualized discussion, but numerous studies provide clinicians confidence in their recommendations (Table). Protocol T demonstrated that first-generation anti-VEGF agents achieve similar outcomes in patients with good baseline VA, allowing treatment choice to be guided by provider-patient discussions.

Protocol V explored whether to begin early treatment in patients with good VA. It found no increased risk of long-term vision loss when initial treatment was deferred, as observation or laser yielded comparable VA outcomes at 2 years.

Since Protocol V, the expanded use of GLP-1 RAs may merit closer monitoring, given a possible association with DME and proliferative diabetic retinopathy. Recently, next-generation anti-VEGF agents have been shown to reduce injection frequency while maintaining visual outcomes. However, further research is needed to understand the role of newer agents in patients with good baseline VA. ■

1. Masahiko S, Takao H, Eiko T, et al. Alteration of treatment choices and the visual prognosis for diabetic macular edema in the era of anti-vascular endothelial growth factor drugs: analysis of the STREAT-DME 2 Study. *Retina*. 2025;45(2):335-344.
2. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193-1203.
3. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123(6):1351-1359.
4. Baker CW, Glassman AR, Beaulieu WT, et al. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA*. 2019;321(19):1880-1894.
5. Chew EY. Patients with good vision and diabetic macular edema involving the center of the macula: to treat or not to treat? *JAMA*. 2019;321(19):1873-1875.
6. Hutton DW, Glassman AR, Stein JD, Bressler NM, Sun JK; DRCR Retina Network. Costs of managing diabetic macular edema with good visual acuity with aflibercept, laser, or observation: DRCR Retina Network Protocol V. *Am J Ophthalmol*. 2021;230:297-302.
7. Hegland TA, Fang Z, Bucher K. GLP-1 medication use for type 2 diabetes has soared. *JAMA*. 2024;332(12):952-953.
8. Wai KM, Mishra K, Koo E, et al. Impact of GLP-1 agonists and SGLT-2 inhibitors on diabetic retinopathy progression: an aggregated electronic health record data study. *Am J Ophthalmol*. 2024;265:39-47.
9. Brown DM, Boyer DS, et al; PHOTON Investigators. Intravitreal aflibercept 8 mg in diabetic macular oedema (PHOTON): 48-week results from a randomised, double-masked, non-inferiority, phase 2/3 trial. *Lancet*. 2024;403(10432):1153-1163.
10. Adrean S. Outcomes of patients with diabetic macular edema (DME) and baseline best-corrected visual acuity (BCVA) of 20/50 or worse or 20/40 or better who were treated with aflibercept 8 mg and 2 mg: a post hoc analysis of the phase 2/3 PHOTON trial. *Invest Ophthalmol Vis Sci*. 2024;65(7):6238.
11. Wong TY, Haskova Z, Asik K, et al. Faricimab treat-and-extend for diabetic macular edema: two-year results from the randomized phase 3 YOSEMITE and RHINE trials. *Ophthalmology*. 2024;131(6):708-723.
12. Ohara H, Harada Y, Hiyama T, Sadahide A, Minamoto A, Kiuchi Y. Faricimab for diabetic macular edema in patients refractory to ranibizumab or aflibercept. *Medicina*. 2023;59(6):1125.
13. Borkar D, Tabano D, Ko S, et al. Real-world clinical and anatomical outcomes in patients with diabetic macular edema treated with faricimab: the FARETINA-DME study. ARVO Annual Meeting; May 5–9, 2024, Seattle.

**GAGE HAZELTON, BA**
- Medical Student, Medical College of Wisconsin, Wausau, Wisconsin
- ghazelton@mcw.edu
- Financial disclosure: None

**DEEPAK SAMBHARA, MD**
- Partner, Medical Director of Research, Medical Retina and Diseases of the Vitreous, Eye Clinic of Wisconsin, Wausau, Wisconsin
- sambhad@eyeclinicwi.com
- Financial disclosure: Advisor/Consultant (4DMT, Abbvie, Adverum, Alcon, Alimera, Alkeus, Annexon, Apellis, Astellas, Coherus, EyePoint, Genentech/Roche, iDocSocial, Ocular Therapeutix, Regeneron); Lecturer (Evolve Medical, iDocSocial, MJH Life Sciences, Vindico Medical Education); Research Funding (4DMT, Adverum, Annexon, Kodiak, Ocular Therapeutix, Opthea); Speaker's Bureau (Apellis, Astellas, Heidelberg, Regeneron); Steering Committee (Ocular Therapeutix, Regeneron); Stock (Eclipse Life Sciences)

# RISING STARS IN RETINA

Retina Today

YoungMD>Connect

## Get to know outstanding retina fellows from the class of 2025.

Michael Yu, MD

***Retina Today (RT):* When did you know that you wanted to become a retina specialist?**

During medical school, before I knew what specialty to pursue, a few classmates persuaded me to attend a talk by Carol L. Shields, MD. That lecture proved to be a serendipitous moment in my medical training, unexpectedly introducing me to ophthalmology and retina. Dr. Shields discussed how a fundus examination revealed choroidal metastases and ultimately led to a diagnosis of esophageal carcinoma. The revelation that the retina could disclose so much about systemic health sparked a fascination with the field that has only grown deeper.

***RT:* Who do you look to as mentors?**

I've had exceptional mentors throughout my training. Dr. Shields was instrumental in guiding me to ophthalmology and exemplifying the profound effect one physician can have on patients and the profession. From residency, my biggest mentors have been Prithvi Mruthyunjaya, MD, MHS; Carolyn Pan, MD; and Quan Dong Nguyen, MD, MSc. More than amazing clinicians, they are also committed to the growth of their trainees, and I can only hope to influence my mentees as profoundly as they have me.

During fellowship, I have learned from the world-class retina team at Wills Eye/Mid Atlantic Retina under the leadership of Carl Regillo, MD; Allen Ho, MD; and Arunan Sivalingam, MD. I consider all the Wills Eye attendings to be my close mentors, particularly Yoshihiro Yonekawa, MD; Omesh Gupta, MD; Jason Hsu, MD; Michael Klufas, MD; David Xu, MD; Anton Orlin, MD; Michael Cohen, MD; Jordan Deaner, MD; Joshua Uhr, MD; Meera Sivalingam, MD; and Samir Patel, MD. From the clinic to the OR, their mentorship continually challenged me to grow and brought out the very best in me.

***RT:* What has been one of the most memorable experiences of your fellowship?**

One of the most rewarding aspects of surgical training is when something finally clicks—when the technique connects or the mechanics become intuitive. In the final months of fellowship, I had more opportunities to staff residents and first-year retina fellows. Watching that same moment of clarity occur for a junior trainee has been such a fulfilling experience. It is a privilege to be part of those breakthroughs, and moments like these fuel my passion for academic medicine.

***RT:* What advice can you offer to residents who are considering retina?**

Retina is an incredibly rewarding subspecialty, offering a balance of complex medical cases and intricate surgical challenges. If you are interested in retina, don't hesitate to put yourself out there—opportunities will come if you seek them. In addition to connecting with attendings, remember to share your interest with your retina fellows, too. As a medical student and resident, I learned so much from my fellows, and those relationships were instrumental in shaping my path. ■

### FIRST CAREER MILESTONE

Dr. Yu is pursuing an ocular oncology fellowship at Moorfields Eye Hospital in London.


**MICHAEL YU, MD**

- Former Vitreoretinal Surgery Fellow, Mid Atlantic Retina, Wills Eye Hospital, and Clinical Instructor, Department of Ophthalmology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- mdyu2020@gmail.com
- Financial disclosure: None



Editorially independent supported by

abbvie

REGENXBIO

# TEACHING FIBROVASCULAR MEMBRANE DISSECTION

## Use this structured approach to teach fellows how to manage complex diabetic eye disease in the OR.

By James Rice, FCOphth(SA), MPH; Thabang Morris, FCOphth(SA); and Jonel Steffen, FCOphth(SA)



Advanced diabetic eye disease produces some of the most challenging cases in vitreoretinal surgery. Fibrovascular proliferation results in complex vitreoretinal adhesions, tractional retinal detachments (RDs), tractional retinoschisis, and combined tractional-rhegmatogenous RDs. Each eye is unique, and surgical strategies need to be dynamic and flexible, with good decision making the key to optimal outcomes.

Teaching and learning fibrovascular tissue dissection in these cases is challenging. Our approach is based on established principles of learning theory. First, ensure a thorough understanding of the pathology of the vitreoretinal interface. On this foundation, build surgical (dexterity) and mental (decision making) skills, and then reinforce the learning with appropriate post-surgical review and audit.

### AT A GLANCE

- Teaching dissection of fibrovascular tissue in diabetic eye disease is challenging; consider using an approach based on established principles of learning theory.
- Break the dissection strategy into clear steps, each with specific goals, and teach the surgical techniques necessary to achieve each step.
- Other steps not discussed here include hemostasis, managing subretinal fluid, laser, and tamponades.
- Have trainees review the surgical video shortly after completing the procedure, and discuss the decisions made during the surgery and other possible options.

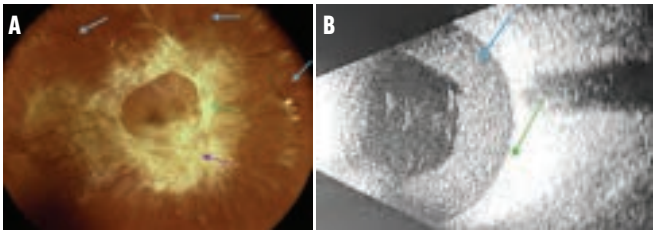



Figure 1. In this color fundus photograph (A), notice the absence of a peripheral PVD, which creates a challenge because it will be difficult to induce a PVD using usual techniques (blue arrows). The image also shows the firm attachment to the optic disc (green arrow) and complex attachments in broad areas of fibrosis (purple arrow). The B-scan ultrasound (B) of a different patient obtained preoperatively shows an extensive posterior hyaloid detachment with a subhyaloid hemorrhage (blue arrow). You can ask trainees to identify the macula (green arrow) and look for traction and adhesions (not present in this image).

## PREOPERATIVE ANALYSIS AND SURGICAL PLANNING

If media clarity allows, perform a preoperative clinical analysis with the trainee. A widefield color image is particularly useful. For example, pockets of subhyaloid hemorrhage will identify focal hyaloid separation. In cases of vitreous hemorrhage, discuss the ultrasound findings. Combining fundus imaging, ultrasound, and possibly OCT can be helpful to analyze and characterize the vitreoretinal interface (Figure 1).

## TEACHING SURGICAL SKILLS

We break the dissection strategy into clear steps, each with specific goals, and teach the surgical techniques necessary to achieve each step. Many techniques can be conceptualized and practiced with simulation. In our practice, we use the Eyesi Surgical Simulator (Haag-Streit GmbH). We recommend that trainers observe and instruct during simulation sessions to maximize the trainee's development. Here are the steps we teach.

### Step No. 1: Access the Correct Surgical Dissection Plane

Following a thorough core vitrectomy and midperipheral trim, identify where best to gain access to the correct surgical plane (the subhyaloid space). In the absence of hyaloid separation, decide where to initiate a focal posterior vitreous detachment (PVD) and which instrument to use (Figure 2).

Commonly, a partial posterior hyaloid separation is present (Figure 3). Be aware that long-standing, preexisting hyaloid separation allows for proliferation of secondary membranes at the hyaloid-retina junction. Unless you identify and lift these, you will fail to find the fibrovascular bridges (pegs) that indicate the correct plane (Figure 4).

### Step No. 2: Extend the Posterior Hyaloid Separation

When the peripheral hyaloid is already detached in one region, or when a new separation has been generated focally using Step 1, the PVD should be actively extended outside the adherent complexes for 360°, if possible. A clear sign that you are in the correct plane is that the peripheral membrane edges start to elevate and mobilize.

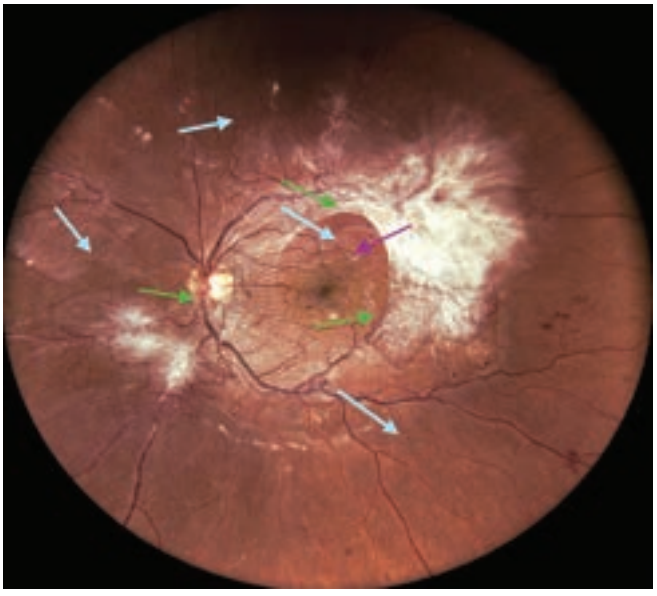


Figure 2. There are several options for gaining access to the correct surgical plane in the absence of a PVD: 1. Use the vitrector if the underlying posterior hyaloid face is loose enough to be elevated by aspiration (usually away from fibrosis; blue arrows); 2. Use forceps to lift a thin fibrotic area with a small circular motion, which may snap weaker attachments and generate a focal separation (often at the edge of fibrosis or near the disc; green arrows); or 3. If the posterior hyaloid face is particularly taut but slightly elevated off the retina, a pick may be most efficient to pierce and open the posterior hyaloid face (usually away from fibrosis; purple arrow).

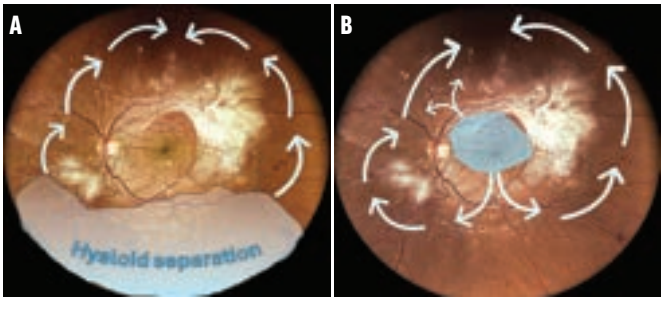



Figure 3. This image highlights a preexisting partial PVD (A) and a generated focal PVD (B). The arrows indicate the desired extension of the hyaloid separation.

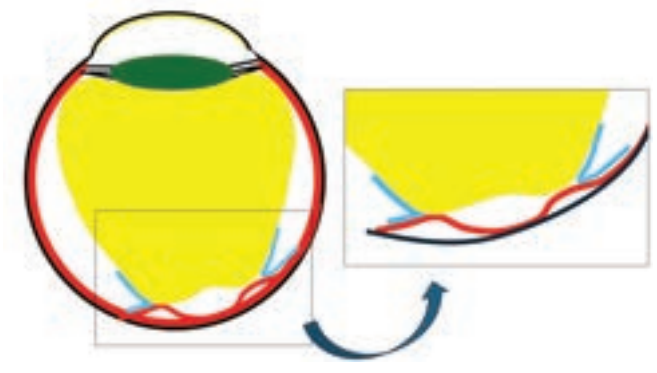


Figure 4. Secondary membranes (blue) must be lifted from the retinal surface to access the dissection plane.

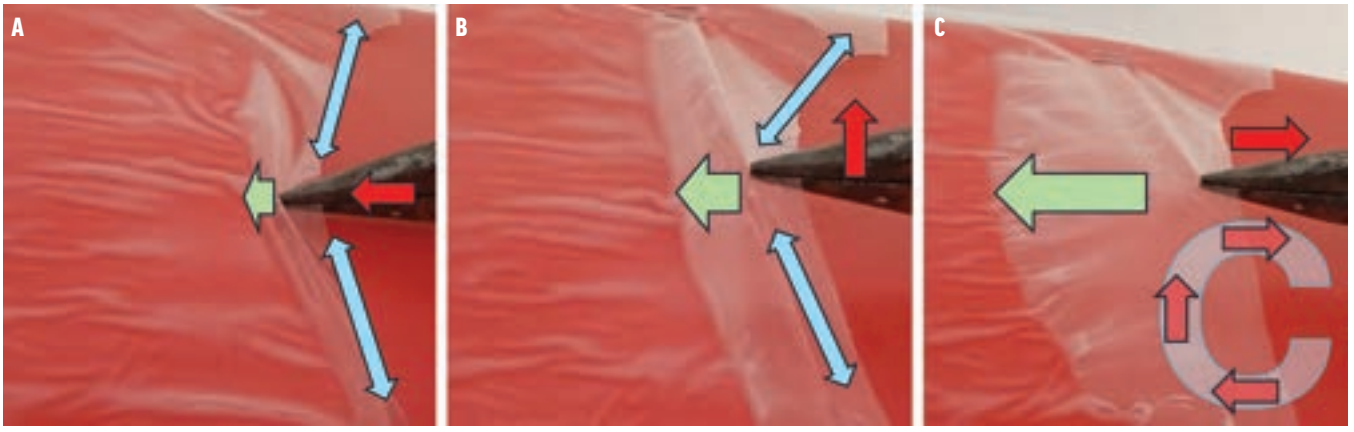



Figure 5. The edge of the hyaloid face is gently held (aspirated) with the vitrector and slowly pulled antegrade (A), vertically (B), and retrograde (C; red arrows), causing the hyaloid detachment to extend (green arrows). The motion limits traction on the adhesions as the distance from the instrument to the adhesions remains relatively constant (blue arrows).

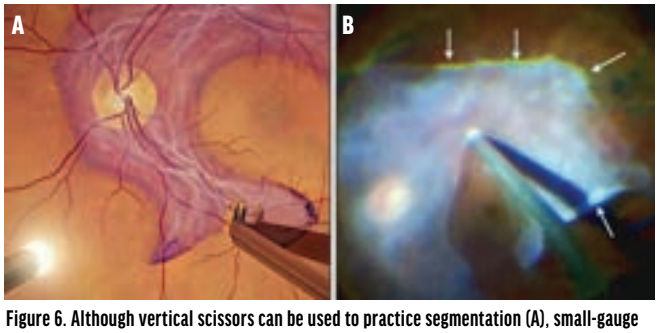



Figure 6. Although vertical scissors can be used to practice segmentation (A), small-gauge beveled cutters are very effective for this step (B). Note the trimmed edges of the membrane following successful 360° peripheral hyaloid separation, and trim (arrows).

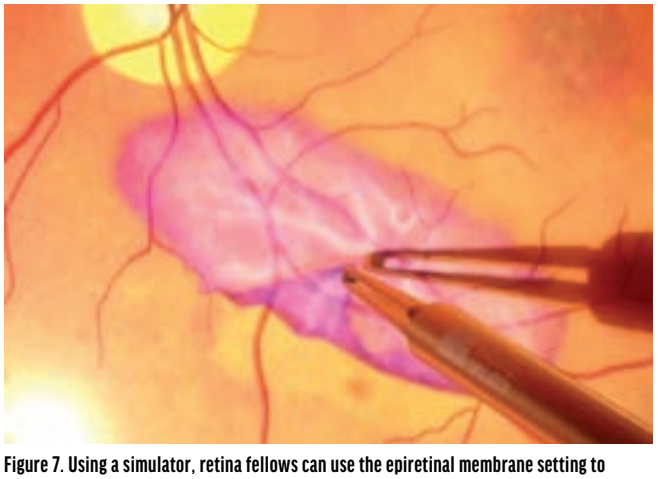


Figure 7. Using a simulator, retina fellows can use the epiretinal membrane setting to explore with forceps.

A useful maneuver to separate the adherent posterior hyaloid face (done in regions without an obvious white fibrovascular complex [FVC], as indicated by the arrows in Figure 3) is to grasp the free-cut edge of the posterior hyaloid face using gentle aspiration of the vitrector and make a slow forward, then anterior, and then retrograde movement, similar to the shape of the letter C (Figure 5). This generates tension on the adherent posterior hyaloid face, causing it to lift for a short distance ahead of the vitrector, while not excessively straining the tight posterior FVC adhesions and vitreous base insertion, limiting the risk of breaks at these locations. The lifted posterior hyaloid face is then removed with the vitrector and the maneuver repeated at the new adherent edge.

Sometimes, thick FVC extending from the posterior pole to the ora serrata may prevent 360° separation. In these cases, segmentation through the fibrotic sheet should ideally be performed to release the anterior-posterior traction.

## Step No. 3: Trim the Loosened Hyaloid and Elevated FVC Edges

A successful peripheral hyaloid separation will result in lifted membrane edges and hyaloid remnants. Trim these with a fold-over technique where the vitrector is positioned on top of the membranes facing the loosened tissue, drawing it in with gentle aspiration and removing it with low risk of retinal breaks.

## Step No. 4: Segment the Residual Posterior Fibrovascular Sheets

If the hyaloid and any secondary membranes at the vitreoretinal junction have been lifted, the correct surgical plane of peg-like adhesions can be accessed. Use the vitrector to segment where possible (Figure 6). We have found that a smaller-gauge beveled cutter can more easily access gaps between adhesions and work closer to the retina. Very small lifting movements (similar to the C-pull) can be useful to open and extend the surgical plane ahead of the cutter.

## Step No. 5: Explore the Edges of Residual Complexes and Consider Removal From the Disc

Use forceps to lift and explore the adhesions of the remaining fibrovascular tissue (Figure 7). This technique may expose more gaps for segmentation or break weaker adhesions. Consider whether the residual complexes need to be removed or left in place and the edges cauterized.

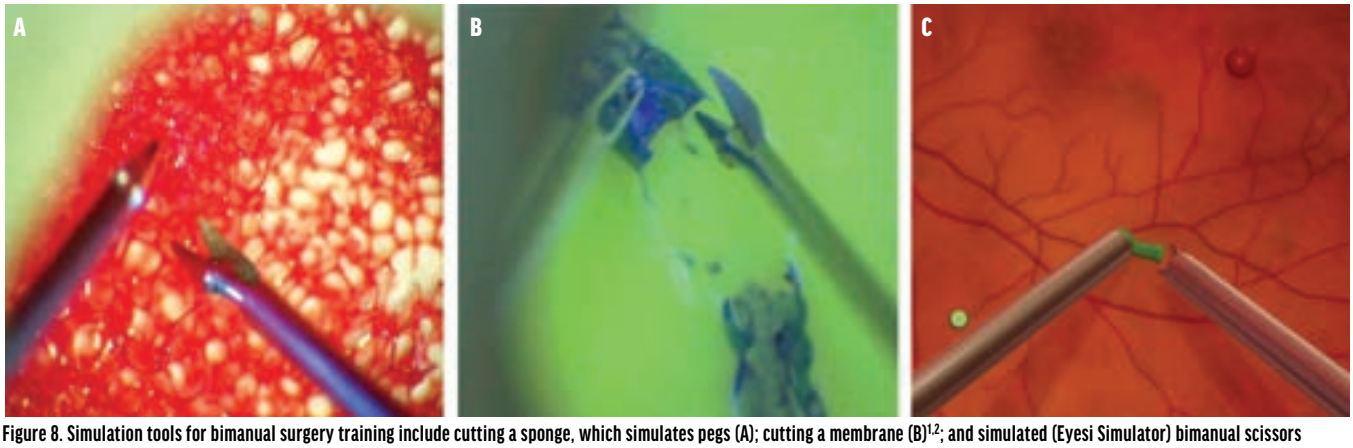



**Figure 8. Simulation tools for bimanual surgery training include cutting a sponge, which simulates pegs (A); cutting a membrane (B)[1,2]; and simulated (Eyesi Simulator) bimanual scissors training without forceps (C).**

Assess the complex attached at the optic disc. If this can be gently removed, it will often reveal small slips of membrane extending over the papillomacular bundle, which will also peel off. If the adhesion to the disc is too strong, leave it attached to avoid disc trauma. In these cases, try to leave the fibrovascular stump long enough for safe cauterization, if needed.

### Step No. 6: Bimanual Surgery

Clinically significant residual membranes (eg, membranes still affecting the macula or adjacent to retinal breaks) can be difficult to remove with one-handed techniques, especially on a detached retina. Bimanual surgery is effective in these complex scenarios. We use end-grasping forceps and curved scissors. The tip of the scissors should not be too sharp, as much of this technique involves using the closed scissors as a spatula to expose the surgical plane around adhesion points. Lift the scissors slightly into the membrane while cutting to avoid damage to the underlying retina or vessel (Figure 8).

Other important steps in diabetic vitrectomy not discussed here include hemostasis, the management of subretinal fluid, laser, and the role of tamponades.

## SIMULATORS ON THE MARKET

In addition to the Eyesi Surgical Simulator (Haag-Streit GmbH), ImmersiveEducation (Immersive Touch) also includes a vitreo-retinal interface. For trainees interested in cataract surgery, the PhacoVision (Melerit Medical), HelpMeSee Eye Surgical Simulator (HelpMeSee), and Fidelis Virtual Reality Ophthalmic Surgical Simulator (Alcon) focus on anterior segment surgery.[1,2]

1. Khullar S, Mishra SK, Joshi A, Sati A, Kumar P, Unni D. Eye on the Future: virtual reality surgical simulator. *Delhi J Ophthalmol*. 2023;33(3):250-254.
2. Soni T, Kohli P. Commentary: Simulators for vitreoretinal surgical training. *Indian J Ophthalmol*. 2022;70(5):1793-1794.

### REVIEW, AUDIT, AND REINFORCE

Review the surgical video shortly after completing the procedure, and discuss the decisions made during the surgery and other possible options. Identify weaker surgical skills and target these for practice.

The trainee should keep a surgical log of individual surgical steps, with proficiency ratings from the trainer, so that areas needing more attention can be identified and addressed. Trainers can also encourage trainees by identifying skills that have improved toward competence. ■

**JAMES RICE, FCOPHTH(SA), MPH**
- Consultant Ophthalmologist, Faculty of Health Sciences, Groote Schuur Hospital and University of Cape Town, Division of Ophthalmology, Cape Town, South Africa
- james.rice@uct.ac.za
- Financial disclosure: None

**THABANG MORRIS, FCOPHTH(SA)**
- Consultant Ophthalmologist and Retinal Fellow, Faculty of Health Sciences, Groote Schuur Hospital and University of Cape Town, Division of Ophthalmology, Cape Town, South Africa
- thabangmorris@gmail.com
- Financial disclosure: None

**JONEL STEFFEN, FCOPHTH(SA)**
- Consultant Ophthalmologist, Faculty of Health Sciences, Groote Schuur Hospital and University of Cape Town, Division of Ophthalmology, Cape Town, South Africa
- j.steffen@uct.ac.za
- Financial disclosure: None

**View this article online to see a table outlining various practice options for fibrovascular membrane dissection.**

# THE PRESSURE IS ON: A CASE OF OCULAR ISCHEMIA


Beware of acute central retinal artery hypoperfusion during pars plana vitrectomy.

BY J. DANIEL DIAZ, MD, AND NINEL Z. GREGORI, MD

Perioperative vision loss in ocular surgery is rare. Among the most common etiologies are retinal vascular ischemia, direct optic nerve trauma during air-fluid exchange or perioperative anesthesia, and nonarteritic anterior ischemic optic neuropathy (NAION).[1] In cases of vision loss related to retinal or optic nerve vascular ischemia, the perfusion pressure of the globe during surgery is essential. Adequate blood flow to organs such as the eye occurs due to a pressure gradient. Here, we present a case in which low intraoperative ocular perfusion pressure secondary to systemic hypotension resulted in transient ocular ischemia (Video).

## CASE REPORT

A 73-year-old man presented with a several-month history of decreased vision in the left eye. Ophthalmic examination was notable for decreased VA to 20/80, a normal anterior segment examination, and evidence of an epiretinal membrane. The patient underwent uncomplicated pars plana vitrectomy (PPV) with epiretinal membrane peeling without internal limiting membrane removal.

Five months following the initial surgery, the patient developed a recurrent epiretinal membrane, and a decision was made to proceed with repeat PPV, epiretinal membrane removal, and additional internal limiting membrane peeling. At the onset of the vitrectomy, progressive optic nerve head pallor, boxcarring of the retinal vessels, and signs of dense retinal ischemia were noted (Figure 1).

Examination of the periorbita revealed no evidence of retrobulbar hemorrhage or orbital compartment syndrome. The decision was made to lower the preset infusion pressure from 30 mm Hg to 10 mm Hg. As machine errors can occur, we also confirmed a low IOP by manually palpating the globe. The patient had a systemic blood pressure of 80/60 mm Hg and a mean arterial pressure of 67 mm Hg. Given the concern for decreased ocular perfusion, intravenous fluids and vasopressors were administered to temporarily increase the patient's mean arterial pressure.

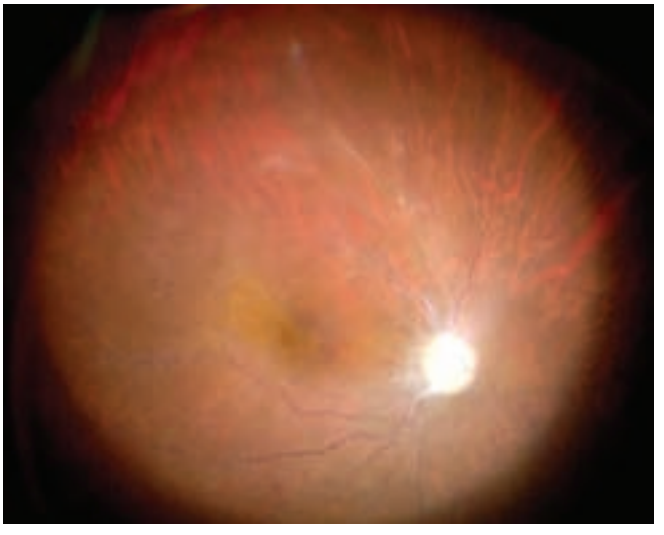


Figure 1. In this intraoperative image, note the dense retinal ischemia.

Over the next several minutes, the patient's systemic blood pressure increased to 110/90 mm Hg, and we noted a return of retinal perfusion (Figure 2). We decided to proceed with PPV and membrane peeling as planned. The rest of surgery was uneventful. At postoperative month 1, the patient's VA was 20/100, with a posterior segment examination revealing evidence of temporal optic nerve head pallor, suggesting the possible development of (NAION).

## DISCUSSION

Maintaining blood flow to all ocular structures during surgery depends on an adequate mean ocular perfusion pressure (MOPP). This is calculated by subtracting the IOP from the mean ophthalmic arterial pressure, which is the mean arterial blood pressure adjusted to the level of the eye.[2] Prolonged alteration of either the IOP or the mean ophthalmic arterial pressure during surgery can lead to ocular ischemia and a risk of permanent vision loss. Most hypothesized mechanisms suggest a link between intraoperative hypotension and/or increased IOP.[3]

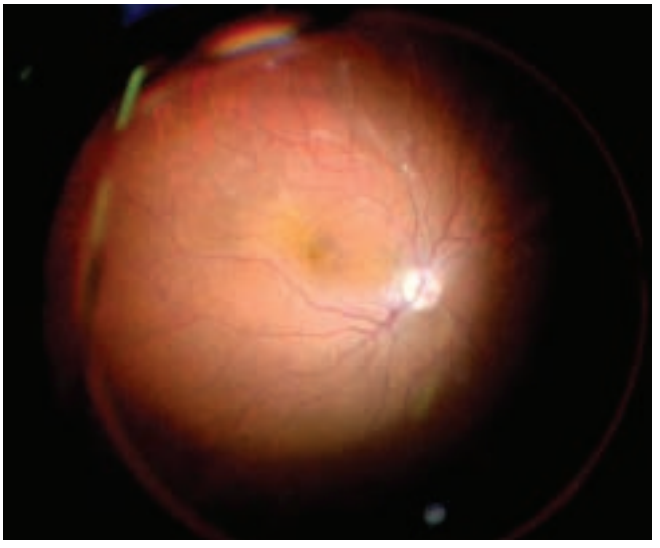


Figure 2. A few minutes after increasing the patient's mean arterial pressure, we noted retinal reperfusion.

Our patient experienced transient retinal ischemia due to intraoperative systemic hypotension, most likely related to anesthetic sedation in the setting of preoperative low blood pressure. He did not have significant cardiovascular comorbidities; however, advanced age and atherosclerotic vascular changes can contribute to altered optic nerve perfusion regulatory mechanisms.[4]

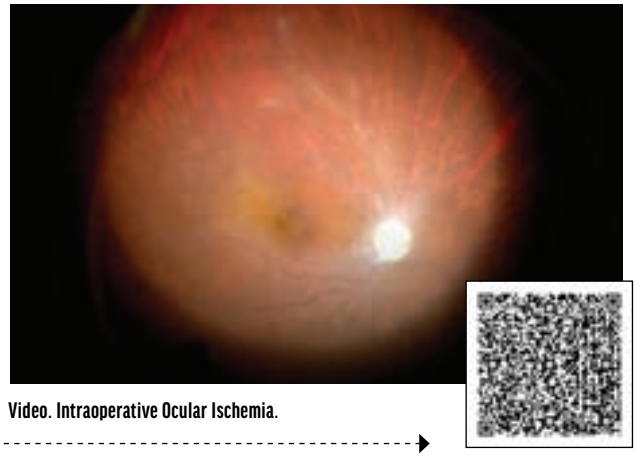
Ellabban et al described the occurrence of a central retinal artery occlusion (CRAO) during vitrectomy that resolved following induction of a posterior vitreous detachment.[5] The researchers thought the cause of the CRAO was related to the local anesthetic bolus and direct compression of the central retinal artery, as there was no evidence of systemic hypotension or elevated IOP. They hypothesized that detaching the hyaloid from the optic disc may have released any abnormal adhesion around the central retinal artery. Suction from the vitreous cutter may have also created a negative pressure force that dislodged a potential thrombus.[5]

Other possible links between local anesthesia and a CRAO during ocular surgery have been described, including elevated IOP with secondary occlusion and a localized vasoconstrictive effect due to adrenaline in the anesthetic.[6]

The temporal optic nerve head pallor noted postoperatively in our patient likely represents the development of ischemic optic neuropathy. NAION is a multifactorial disease resulting from hypoperfusion of the prelaminar optic nerve head. NAION following vitrectomy has been reported, and while exact mechanisms are unclear, it is likely that decreased ocular perfusion pressure during surgery precipitated ischemia of the anterior optic nerve. Other factors contributing to NAION after vitreoretinal surgery may include direct optic nerve head trauma due to stretching and elongation of axons during the separation of the posterior hyaloid.

Rossi et al used a novel device to calculate the MOPP during PPV.[2] The authors reported both a reduction in the mean arterial pressure due to anesthetic sedation and periods of increased IOP throughout surgery. This combination resulted in a reduction in the MOPP below critical limits, placing the eye at risk of ischemic damage due to limited autoregulation at the level of the optic nerve head. Prior studies have also measured intraoperative IOP during a variety of procedures, including cataract extraction and scleral buckle placement.

WATCH IT NOW



Video. Intraoperative Ocular Ischemia.

It is critical to remain vigilant of the retinal and optic nerve perfusion pressure during vitrectomy and to balance the intraocular infusion pressure against the blood pressure. The typical infusion cannula pressure may need to be reduced to improve optic nerve and retinal perfusion pressure. The best way to maintain an adequate MOPP is likely appropriate control of IOP during intraocular surgery; however, increased intravenous fluids and vasopressors may be needed in cases of extremely low blood pressure under sedation. ■

1. Jain N, McCuen BW 2nd, Mruthyunjaya P. Unanticipated vision loss after pars plana vitrectomy. Surv Ophthalmol. 2012;57(2):91-104.
2. Rossi T, Querzoli G, Gelso A, et al. Ocular perfusion pressure control during pars plana vitrectomy: testing a novel device. *Graefes Arch Clin Exp Ophthalmol*. 2017;255(12):2325-2330.
3. Hayreh SS. Ischemic optic neuropathies - where are we now? *Graefes Arch Clin Exp Ophthalmol*. 2013;251(8):1873-1884.
4. Riva CE, Hero M, Titze P, Petrig B. Autoregulation of human optic nerve head blood flow in response to acute changes in ocular perfusion pressure. *Graefes Arch Clin Exp Ophthalmol*. 1997;235(10):618-626.
5. Ellabban AA, Patil AD, Costen MT, Babar AR. Central retinal artery occlusion during vitrectomy: Immediate retinal revascularization following induction of posterior vitreous detachment. *Am J Ophthalmol Case Rep*. 2018;9:38-40.
6. Swamy BN, Merani R, Hunyor A. Central retinal artery occlusion after phacoemulsification. *Retin Cases Brief Rep*. 2010;4(3):281-283.

**J. DANIEL DIAZ, MD**
- Vitreoretinal Surgeon, Retina Consultants of Miami, Miami
- Financial disclosure: None

**NINEL Z. GREGORI, MD**
- Professor of Clinical Ophthalmology and Lois Pope Endowed Chair for Age-Related Macular Degeneration Research, Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami
- Chief of Ophthalmology Section, Miami Veterans Affairs Medical Center, Miami
- ngregori@med.miami.edu
- Financial disclosure: None

# CODING ADVISOR

A Collaboration Between *Retina Today* and AMERICAN ACADEMY OF OPHTHALMOLOGY

# ASK THE EXPERT: COMMON RETINA CODING QUESTIONS

Knowing the answers could mean the difference between a successful claim and a denial.

BY JOY WOODKE, COE, OCS, OCSR

Retina coding can often feel complex and challenging, but it doesn't have to be. Here, I share a few of the most important questions that have been asked, and the answers that can help you expand your coding knowledge.

### Q: IS IT APPROPRIATE TO UNBUNDLE AN ANTERIOR CHAMBER (AC) TAP—CPT CODE 65800, PARACENTESIS OF AC OF EYE (SEPARATE PROCEDURE), WITH REMOVAL OF AQUEOUS—WHEN PERFORMED IN THE SAME SESSION AS AN INTRAVITREAL INJECTION, CPT CODE 67028?

**A:** CPT code 65800 is bundled with 67028 under the National Correct Coding Initiative. It should not be unbundled when performed on the same eye during the same encounter, as it does not meet the criteria for using modifier -59 because the AC tap is typically prophylactic.

### Q: IS IT APPROPRIATE TO ORDER OCT ANGIOGRAPHY IN ADDITION TO RETINA OCT ON ALL PATIENTS AND BILL THE HIGHER REIMBURSING CODE, CPT CODE 92137, EVEN THOUGH THE RETINA OCT GUIDES DECISION MAKING?

**A:** OCT alone can typically be used to monitor anti-VEGF treatment, so an additional test (CPT code 92137) requires additional documentation that supports medical necessity and explains how this test will guide medical decision making and the patient's treatment. For example, OCT angiography can be medically necessary in some instances to document the progression of choroidal neovascularization.

### Q: DOES THE MEDICARE ADMINISTRATIVE CONTRACTOR PALMETTO GBA REQUIRE A PATIENT WITH DIABETES TO BE DIAGNOSED WITH RETINOPATHY TO BILL AN ANNUAL FUNDUS PHOTOGRAPH?

**A:** Palmetto has both a local coverage determination (LCD) and a local coverage article (LCA) for fundus photography. Copies of current LCDs/LCAs can be found on each payer's website and at aao.org/lcds.

Palmetto's LCD (L33467) states that fundus photography is not covered for routine screening and provides guidelines to meet medically necessary coverage. However, the policy does confirm that fundus photography is considered medically necessary when "monitoring potential progression of a disease process" such as diabetes.

The LCA (A53060) confirms that fundus photography can be medically necessary to monitor diabetes without retinopathy or diabetic macular edema and provides ICD-10-CM codes that support medical necessity, including E10.9, type 1 diabetes without complications, and E11.9, type 2 diabetes without complications.

### Q: DUE TO OUR COMPOUNDING PHARMACY'S SHORTAGE OF COMPOUNDED ANTIBIOTICS, WE ADMINISTER INJECTIONS OF VANCOMYCIN AND CEFTAZIDIME FROM RECONSTITUTED POWDER-FILLED VIALS. HOW DOES THIS AFFECT OUR CODING?

**A:** After being reconstituted, the drug has a shorter shelf life. Bill as single-use vials per the label. Bill each medication's specific HCPCS code and include the National Drug Code (NDC) from the vial.

When reporting reconstituted medications, the unit of measure (UOM) reported in item 24a following the NDC should be the total number of vials used (eg, UN1 = one vial used). This is different than a liquid vial of medication where the UOM is reported in terms of volume (eg, 2 mg/0.05 mL = ML0.05).

The HCPCS dosage (unit) for ceftazidime is 500 mg. Any amount up to 500 mg is reported as one billing unit.

**OCT ALONE CAN TYPICALLY BE USED TO MONITOR ANTI-VEGF TREATMENT, SO AN ADDITIONAL TEST (CPT CODE 92137) REQUIRES ADDITIONAL DOCUMENTATION THAT SUPPORTS MEDICAL NECESSITY AND EXPLAINS HOW THIS TEST WILL GUIDE MEDICAL DECISION MAKING AND THE PATIENT'S TREATMENT.**

If a single-use vial has 500 mg, bill one unit injected and report the -JZ modifier because the remaining drug is less than one unit. Documentation should include the actual dosage in mg/mL injected and state that the remaining medication less than one unit was discarded. Medicare (as well as other payers) has policies that state to purchase the vial size that minimizes waste.

Effective July 1, 2025, HCPCS code J3370—injection, vancomycin, 500 mg—was discontinued, and a new code, J3373—injection, vancomycin, 10 mg—was added. If the dosage is 10 mg or less, bill one unit.

### Q: WE HAVE A PATIENT WHO WAS GIVEN AN INTRAVITREAL INJECTION OF COMPOUNDED GANCICLOVIR–CPT CODE 67028. IT WAS PREPARED IN A PRE-FILLED SYRINGE BY A COMPOUNDING PHARMACY. THE DOSAGE WAS 2 MG, WHICH IS DIFFERENT THAN THE GANCICLOVIR IMPLANT. HOW DO WE CODE THE MEDICATION?

**A:** Report as HCPCS code J7999—compounded medication—and include the medication name, dosage, and invoice amount in item 19 of the CMS-1500 form.

### Q: WE PURCHASED BEVACIZUMAB (AVASTIN, GENENTECH/ROCHE) FROM A COMPOUNDING PHARMACY. FOR BILLING PURPOSES, SHOULD WE USE THE NDC NUMBER ON THE REPACKAGED SYRINGE OR THE NDC NUMBER FOR THE MEDICATION?

**A:** Report NDC 50242-0060-01. Correct billing is based on the medication NDC prior to repackaging. The NDC from a compounding pharmacy is for tracking, not billing, purposes. Reporting it on a claim will prompt a denial.

### Q: WHEN BILLING FOR SILICON-FREE REPACKAGED BEVACIZUMAB, THE SYRINGES COME WITH 2.5 MG/0.1 ML, BUT ONLY 1.25 MG IS INJECTED INTO THE EYE. SHOULD THE REMAINING 1.25 MG BE BILLED WITH THE APPROPRIATE HCPCS CODE AND MODIFIER -JW?

**A:** The silicone-free syringes are prepared with overfill to allow the needle to be primed prior to the injection. Overfill, according to Medicare, is not considered wastage and should not be reported with modifier -JW. Include in your documentation the dosage injected and that the overfill medication was discarded.

### Q: WHEN CPT CODE 67105–LASER REPAIR OF A RETINAL DETACHMENT–IS PERFORMED THE SAME DAY AS THE EXAMINATION, WHICH MODIFIER SHOULD BE APPENDED, -25 OR -57?

**A:** Modifier -57 is appended to office visits the same day as or a few days prior to a major surgery (90-day global period). It indicates that the office visit includes the decision for the major procedure.

Modifier -25 is appended to an office visit the same day as a minor surgery (0- or 10-day global period) if it is a significant, separately identifiable evaluation and management service by the same physician on the same day of the procedure or other service.

CPT code 67105—repair of retinal detachment, including drainage of subretinal fluid when performed, photocoagulation—has a 10-day global period. If the examination meets the definition of modifier -25, then append it to the office visit code.

### Q: DOES THE 28-DAY FREQUENCY LIMITATION APPLY TO INTRAVITREAL INJECTIONS, CPT CODE 67028, ONLY WHEN ONE EYE IS BEING TREATED OR WHEN BOTH EYES ARE BEING TREATED BUT ON DIFFERENT DATES OF SERVICE?

**A:** Treatment frequency is based on the FDA label of each drug, which isn't always 28 days. When treating both eyes, injections can occur on different days within the same limited period if performed on opposite eyes. Newer drugs have varied frequency limitations per indication and can have dosing flexibility.

### LEARN MORE

To find more information on retina coding, visit the AAO's dedicated site, aao.org/coding, and check out the *Retina Coding: Complete Reference Guide.* ■

**JOY WOODKE, COE, OCS, OCSR**
- Director of Coding & Reimbursement, American Academy of Ophthalmology, San Francisco
- jwoodke@aao.org
- Financial disclosure: None

# IMMUNOSUPPRESSIVE THERAPY FOR SEVERE NONINFECTIOUS CHOROIDITIS

These cases illustrate the value of not hesitating to begin aggressive treatment.

BY CARL P. HERBORT JR, MD, PD, AND IOANNIS PAPASAVVAS, MD

Several forms of noninfectious choroidites—including idiopathic multifocal choroiditis (MFC), serpiginous choroiditis (SC), Vogt-Koyanagi-Harada disease (VKH), and *HLA-A29* birdshot retinochoroiditis—can have a deleterious evolution if early, prolonged immunosuppressive treatment is not applied.[1,2] The pattern of treatment typically comprises multiple steroidal and nonsteroidal immunosuppressive agents or biologic agents. The most frequently used therapeutics in our clinic are prednisone (for short-term use), azathioprine, cyclosporine, tacrolimus, mycophenolic acid, and, rarely, methotrexate or biologics (ie, anti-TNF-α antibodies, anti-IL-6 antibodies, or rituximab).[3] The most reliable biomarker for determining the treatment course and monitoring effectiveness is ICG angiography (ICGA), as only ICGA can precisely show stabilization of severe choriocapillaritis or choroidal stromal inflammation.[4]

This article examines each of these vision-threatening choroidites and details cases in which aggressive immunosuppression was applied with good visual outcomes.

## CASE NO. 1: MFC

A 46-year-old woman presented for emergency care complaining of photopsias and scotomas. She had experienced a similar episode 17 years earlier, which had been treated after a delay, resulting in a significant decrease in vision. She presented with ill-defined peripapillary

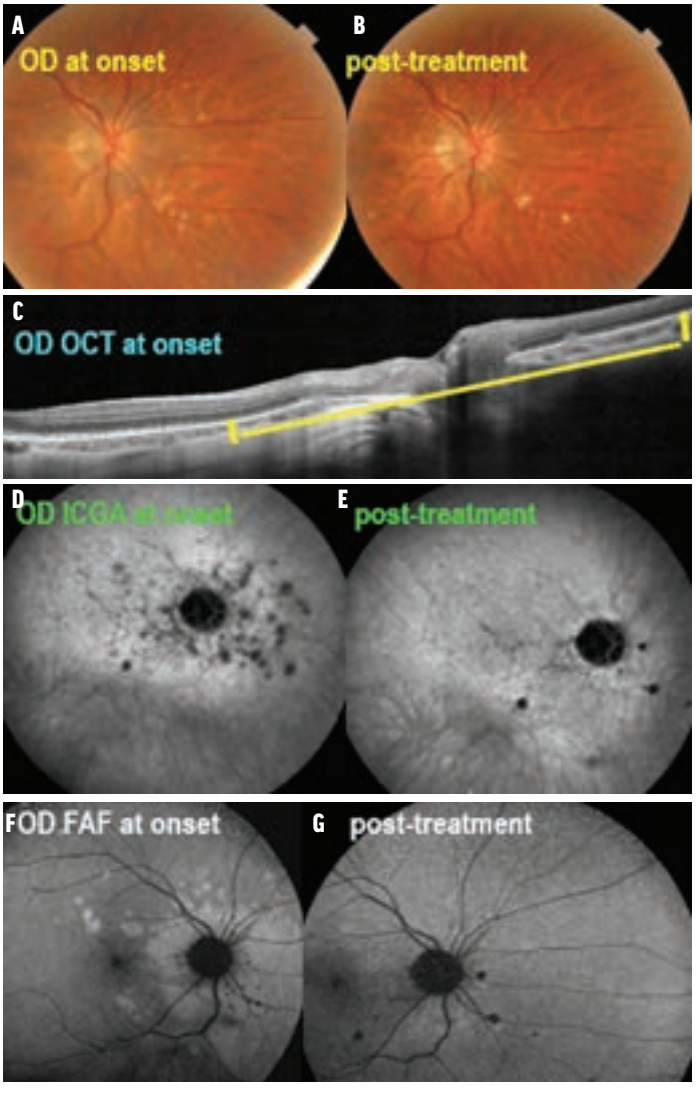



Figure 1. The peripapillary foci present at onset (A) regressed after treatment, leaving only three small, punched-out chorioretinal scars (B). OCT at presentation showed outer segment loss (yellow line) corresponding to the areas of hyperautofluorescence (C). Numerous hypofluorescent occult (ie, not seen on fluorescein angiography) lesions on ICGA (D) resolved after treatment, leaving only three hypofluorescent scars (E). Peripapillary fundus hyperautofluorescence resolved after treatment (F, G).

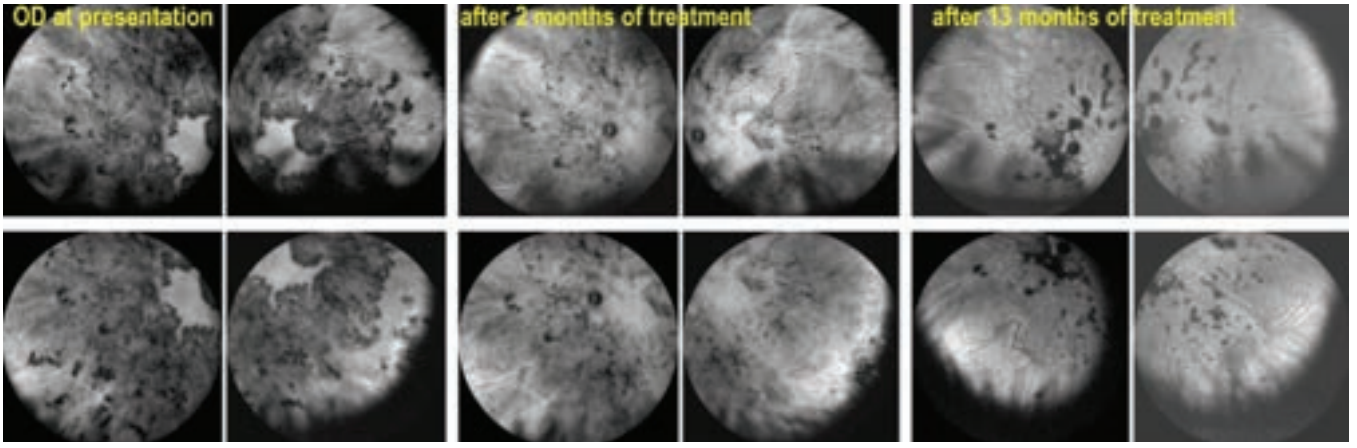



Figure 2. Extended areas of choriocapillaris nonperfusion were noted at presentation. After 2 months of immunosuppressive treatment and anti-TB therapy, substantial reperfusion of the choriocapillaris was apparent. Additional reperfusion of the choriocapillaris was noted at 13 months; the remaining dark areas correspond to chorioretinal atrophic scars.

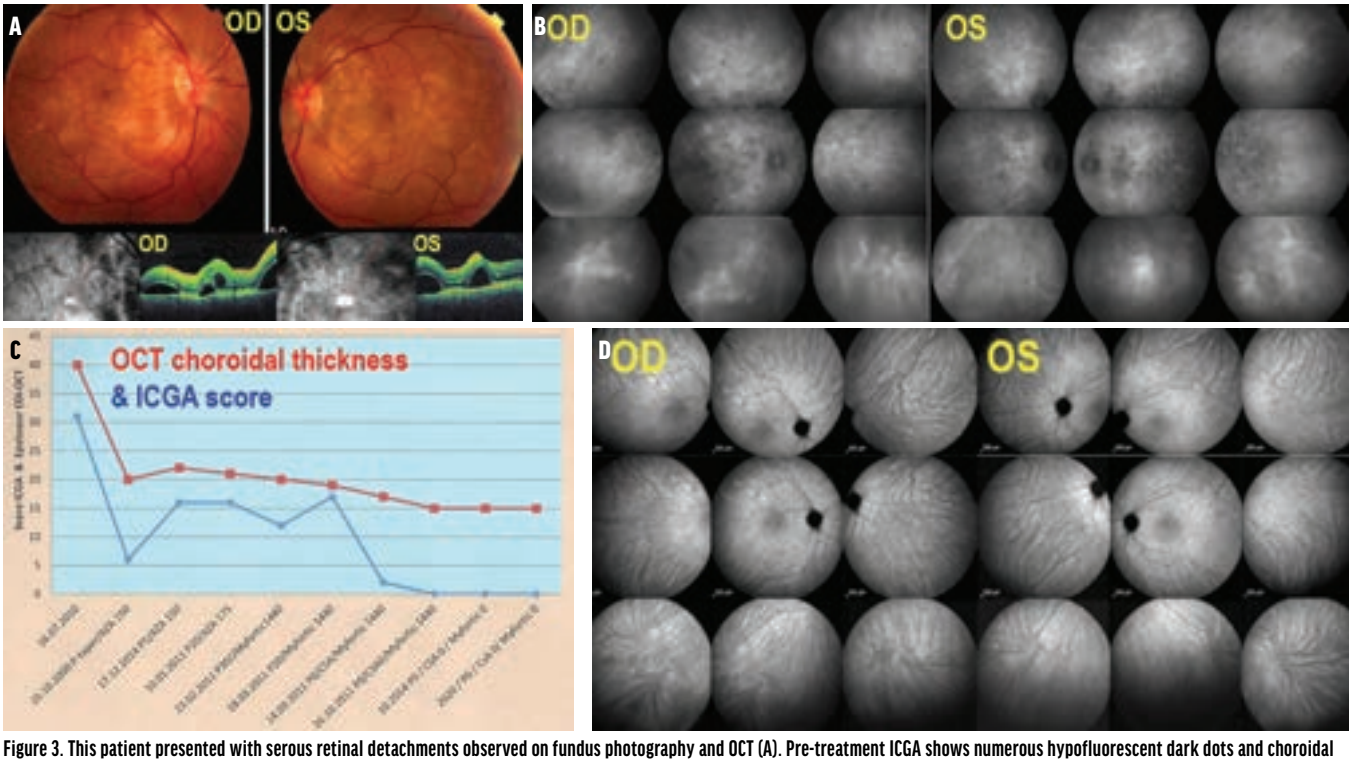



Figure 3. This patient presented with serous retinal detachments observed on fundus photography and OCT (A). Pre-treatment ICGA shows numerous hypofluorescent dark dots and choroidal vasculitis (fuzzy indistinct vessels; B). The graph (C) shows the fine-tuning of immunosuppressive therapy according to the ICGA angiographic score (blue line); the red line indicates choroidal thickness measured by OCT, an unreliable biomarker to monitor disease evolution. After 8 years of follow-up, the choroidal stroma remained inflammation-free (D).

chorioretinal lesions on fundus photography, numerous hypofluorescent spots on ICGA, peripapillary hyperautofluorescence on fundus autofluorescence (FAF), areas of photoreceptor loss in the outer segments on OCT, and a peripapillary scotoma on visual field (VF) testing (Figure 1).

The patient received prednisone tapered over 6 months, cyclosporine tapered over 13 months, and mycophenolic acid tapered over 21 months. After 21 months, the fundus foci, ICGA lesions, and FAF findings had resolved except for rare punched-out scars. Her functional visual acuity was retained, and her VF had normalized.

## CASE NO. 2: SC

A 38-year-old man with bilateral tuberculosis-related SC (TB-SC) who was treated sequentially with prednisone monotherapy and then with anti-TB antibiotherapy, which did not halt the progression of disease. However, the disease responded to a combination of multiple immunosuppressants (prednisone, cyclosporine, and infliximab) and anti-TB quadritherapy. ICGA showed substantial reperfusion of the occluded choriocapillaris (Figure 2). The total duration of immunosuppressive therapy was 36 months, and the duration of anti-TB therapy was 14 months.

SC is the most aggressive form of choriocapillaritis, resulting in extensive chorioretinal scars if not managed diligently. Treatment with multiple immunosuppressive agents has been robustly advocated.[5-11] For all cases of SC with possible TB involvement, *Bacilli* infection must be ruled out by performing an interferon-gamma release assay; if the result is positive, the case should be considered TB-SC. Such cases not only require multiple immunosuppressive treatments, but also concomitant antibiotics to treat the TB.[12]

## CASE NO. 3: VKH

A 38-year-old woman with findings indicating acute VKH was treated early (ie, within 2 weeks of first symptoms) with triple immunosuppressants: prednisone tapered for 13 months, cyclosporine tapered for 15 months, and mycophenolic acid for 51 months (Figure 3). The patient was followed for 8 years and remained recurrence-free without treatment.

If early, prolonged ICGA-assisted treatment with steroidal and nonsteroidal immunosuppressive agents is not applied, acute VKH is likely to evolve into chronic disease with a relentless course and risk of various complications, including sunset glow fundus, cataract, glaucoma, and subretinal fibrosis.[13] Treatment with multiple immunosuppressive agents and ICGA-controlled tapering until absence of stromal choroidal inflammation can prevent chronic evolution and sunset glow fundus depigmentation and enhance the prospect of treatment-free resolution.[14-16]

## ACT DECISIVELY TO PRESERVE VISION

The range of immunosuppressive/immunomodulatory agents available has expanded substantially in parallel with the availability of precise imaging biomarkers for choroidal inflammatory activity, such as ICGA. Such advances have allowed for better fine-tuning of immunosuppressive management. For these vision-threatening conditions, ophthalmologists should consider the use of immunosuppressive therapy with multiple agents. ■


1. Herbort CP Jr, Mantovani A, Tugal-Tutkun I, Papasavvas I. Classification of non-infectious and/or immune mediated choroiditis: a brief overview of the essentials. *Diagnostics (Basel)*. 2021;11(6):939.
2. Neri P, Herbort CP Jr, Hedayatfar A, et al. "White dot syndromes," an inappropriate and outdated misnomer. *Int Ophthalmol*. 2022;42(1):1-6.
3. Papasavvas I, Tugal-Tutkun I, Herbort CP Jr. Mechanisms, pathophysiology and current immunomodulatory/immunosuppressive therapy of non-infectious and/or immune-mediated choroiditis. *Pharmaceuticals (Basel)*. 2022;15(4):398.
4. Papasavvas I, Tucker WR, Mantovani A, Fabozzi L, Herbort CP Jr. Choroidal vasculitis as a biomarker of inflammation of the choroid: indocyanine green angiography (ICGA) spearheading for diagnosis and follow-up, an imaging tutorial. *J Ophthalmic Inflamm Infect*. 2024;14(1):63.
5. Hooper PL, Kaplan HJ. Triple agent immunosuppression in serpiginous choroiditis. *Ophthalmology*. 1991;98(6):944-51;discussion 951-952.
6. Akpek EK, Baltatzis S, Yang J, Foster CS. Long-term immunosuppressive treatment of serpiginous choroiditis. *Ocul Immunol Inflamm*. 2001;9(3):153-167.
7. Nazari Khanamiri H, Rao NA. Serpiginous choroiditis and infectious multifocal serpiginoid choroiditis. *Surv Ophthalmol*. 2013;58(3):203-232.
8. Markomichelakis NN, Halkiadakis I, Papaeythymiou-Orchan S, Giannakopoulos N, Ekonomopoulos N, Kouris T. Intravenous pulse methylprednisolone therapy for acute treatment of serpiginous choroiditis. *Ocul Immunol Inflamm*. 2006;14(1):29-33.
9. Venkatesh P, Tayade A, Gogia V, Gupta S, Shah BM, Vohra R. Short-term intensive immunosuppression: a randomized, three-arm study of intravenous pulse methylprednisolone and cyclophosphamide in macular serpiginous choroiditis. *Ocul Immunol Inflamm*. 2018;26(3):469-476.
10. Ebrahimiadib N, Modjtahedi BS, Davoudi S, Foster CS. Treatment of serpiginous choroiditis with chlorambucil: a report of 17 patients. *Ocul Immunol Inflamm*. 2018;26(2):228-238.
11. Chinchurreta Capote A, Requena Jiménez JM, Lorenzo Soto M, Romero Gómez C, García de Lucas MD. Effectiveness of adalimumab for refractory serpiginous choroiditis. *Ocul Immunol Inflamm*. 2014;22(5):405-408.
12. Papasavvas I, Jeannin B, Herbort CP Jr. Tuberculosis-related serpiginous choroiditis: aggressive therapy with dual concomitant combination of multiple anti-tubercular and multiple immunosuppressive agents is needed to halt the progression of the disease. *J Ophthalmic Inflamm Infect*. 2022;12(1):7.
13. Al-Kharashi AS, Aldibhi H, Al-Fraykh H, Kangave D, Abu El-Asrar AM. Prognostic factors in Vogt-Koyanagi-Harada disease. *Int Ophthalmol*. 2007;27(2-3):201-210.
14. Abu El-Asrar AM, Dosari M, Hemachandran S, Gikandi PW, Al-Muammar A. Mycophenolate mofetil combined with systemic corticosteroids prevents progression to chronic recurrent inflammation and development of 'sunset glow fundus' in initial-onset acute uveitis associated with Vogt-Koyanagi-Harada disease. *Acta Ophthalmol*. 2017;95(1):85-90.
15. Herbort CP Jr, Abu El Asrar AM, Yamamoto JH, et al. Reappraisal of the management of Vogt-Koyanagi-Harada disease: sunset glow fundus is no more a fatality. *Int Ophthalmol*. 2017;37(6):1383-1395.
16. Herbort CP Jr, Abu El Asrar AM, Takeuchi M, et al. Catching the therapeutic window of opportunity in early initial-onset Vogt-Koyanagi-Harada uveitis can cure the disease. *Int Ophthalmol*. 2019;39(6):1419-1425.



**CARL P. HERBORT JR, MD, PD**
- Retinal and Inflammatory Eye Diseases, Centre for Ophthalmic Specialized Care, Lausanne, Switzerland
- Financial disclosure: None

**IOANNIS PAPASAVVAS, MD**
- Retinal and Inflammatory Eye Diseases, Centre for Ophthalmic Specialized Care, Lausanne, Switzerland
- Financial disclosure: None


## CASE NO. 4: BIRDSHOT RETINOCHOROIDITIS

Follow the QR code to learn more about a 45-year-old woman with stromal choroiditis due to *HLA-A29* birdshot retinochoroiditis (Figure) who was treated with periocular steroids and mycophenolic acid for 6 months without satisfying efficacy.

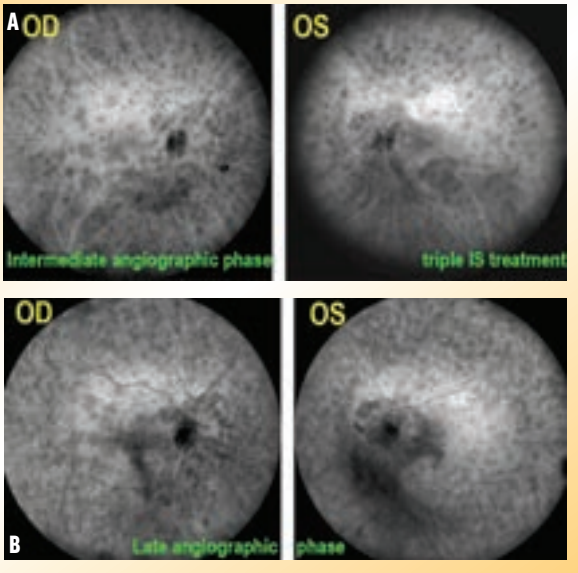



**Figure. This patient was treated for 12 months with periocular steroids, mycophenolic acid, and infliximab with numerous persistent hypofluorescent dark dots and choroidal vasculitis with an unrecognizable course of choroidal vessels both in the intermediate (A) and late angiographic phases (B).**

# REDUCING CHEMOTHERAPY DURATION FOR HIGH-RISK RETINOBLASTOMA

Three cycles may offer comparable clinical benefit to six cycles while reducing treatment burden.

BY MADISON M. WOODS, BA; ROBERT J. MEDINA, BA; AND CAROL L. SHIELDS, MD

Retinoblastoma is the most common intraocular malignancy in children.[1] Those who present with retinoblastoma invasion into the optic nerve beyond the lamina cribrosa and those with choroidal invasion > 3 mm are at a higher risk for metastatic disease; such cases are classified as high-risk retinoblastoma (Figure).

To reduce metastatic retinoblastoma in children with high-risk histopathological features (HRFs), enucleation is performed, after which, HRFs are confirmed by histopathology. Subsequent adjuvant chemotherapy is then delivered to reduce metastatic potential.[2] Although six cycles of chemotherapy with vincristine, etoposide, and carboplatin (VEC) is the standard protocol in such cases,[2,3] a recent study has demonstrated a noninferior therapeutic benefit after only three cycles. This article reviews the literature supporting this novel three-cycle protocol, as well as potential reasons to exercise caution in adopting a standard regimen.

## CURRENT THERAPEUTIC STANDARD

Honavar et al conducted an important retrospective comparative study including 1,020 children with retinoblastoma, of whom 80 had unilateral sporadic disease and were found on histopathology to have HRF.[2] The study authors found that 46 children (58%) received adjuvant treatment with a variety of chemotherapeutic agents (some with additional radiotherapy), while 34 (42%) did not receive any form of adjuvant therapy. Those who received adjuvant chemotherapy experienced only 4% metastasis versus 24% in those who received no adjuvant therapy ($P = .02$).[2] This report stimulated the use of chemotherapy for the treatment of cases with demonstrated HRF.

Kaliki et al later evaluated the effects of a specific chemotherapy regimen of VEC for six cycles for HRF following enucleation for retinoblastoma and noted complete success, with no cases of metastatic disease.[3]

## THREE VERSUS SIX

In 2024, Ye et al performed a dual-institution randomized clinical trial involving 179 patients with unilateral retinoblastoma who all underwent enucleation and were found to have HRF. The study compared three versus six cycles of VEC as adjuvant chemotherapy,[4] focusing on eyes with HRF as defined by the American Joint Committee on Cancer's pathologic staging: pT3a (massive choroidal infiltration), pT3b (retrolaminar optic nerve invasion), and pT3c (scleral invasion).[5] Of this group, 89 patients (49.7%) received three cycles of VEC and 90 (50.3%) received six cycles. The three-cycle regimen was delivered over 9 weeks, while the six-cycle regimen spanned 18 weeks.[4]

The results demonstrated noninferiority of the three-cycle when comparing 5-year disease-free survival (90% vs 89% in the three- and six-cycle groups, respectively) and overall survival (92% vs 89% in the three- and six-cycle groups, respectively). Between groups, grade 3 and 4 toxic effects showed no significant difference (10% vs 13% in the three- and six-cycle groups, respectively). In addition, the authors reported lower direct and indirect costs associated with the three-cycle group. They found that three-cycle VEC adjuvant chemotherapy was as effective as six cycles in preventing metastasis and death, with fewer treatment-related adverse effects and lower cost to patients. Therefore, the authors suggested that a three-cycle regimen of VEC could serve as a new standard, replacing the existing six-cycle treatment regimen.[4]

Ye et al also used a shorter interval between cycles (21 vs 28 days), which led to a total therapy of only 63 days for the three-cycle group versus 126 days for the six-cycle group.[4]

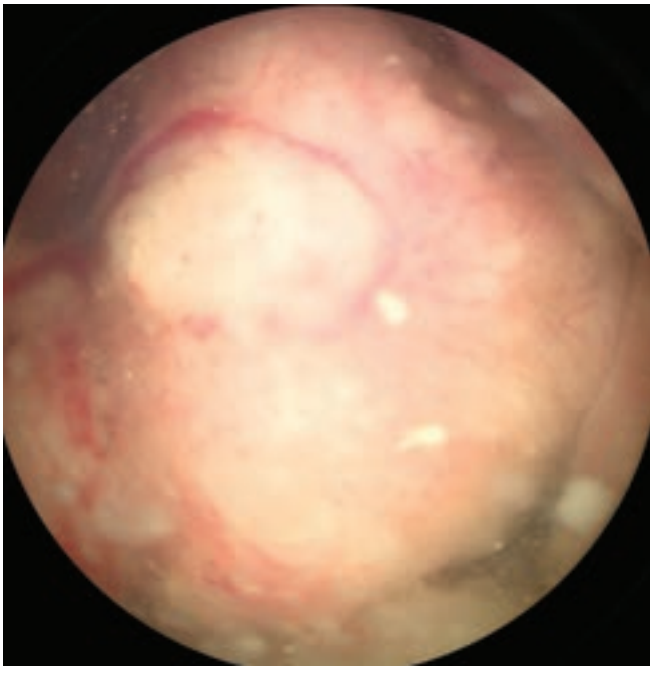


Figure. Fundus photography demonstrates a case of invasive retinoblastoma.

## DEBATE AROUND THREE-CYCLE ADJUVANT CHEMOTHERAPY

Leahey et al agreed that the shortened three-cycle/9-week chemotherapy for HRF in enucleated retinoblastoma could be comparable with the current six-cycle/24-week standard.[6] These authors emphasized that Ye et al's findings underscore the importance of providing adjuvant therapy for HRF despite negative surgical margins.[6]

However, they also pointed out that applying these findings to those needing adjuvant therapy after secondary enucleation following previous chemotherapy could lead to the downstaging of pathological HRF and extraocular extension, potentially increasing the risk of metastatic death.[6] It should be noted that the study by Ye et al excluded patients with prior retinoblastoma treatment.[4]

Chantada et al further cautioned that this new information should not yet be widely considered, as patients with HRF retinoblastoma are at a heterogeneous risk for the development of extraocular relapse.[7] Two groups were used to demonstrate the extremes of these treatment differences: 1) patients with isolated massive choroidal infiltration (ie, pT3a), who maintained a high 5-year overall survival rate in the absence of VEC chemotherapy, implying that treatment might not be necessary in select cases; and 2) patients with a more extensive clinical picture of combined post-laminar optic nerve and massive choroidal invasion with peripapillary invasion who have less-than-optimal 5-year disease-free survival rates despite treatment with the current standard of six cycles of adjuvant chemotherapy, suggesting current treatment practices may need an intensification rather than a reduction.

Thus, a three-cycle adjuvant chemotherapy standard may not be appropriate in all cases; treatment duration should be optimized based on individual patient presentations.[7]

## WORTH INVESTIGATING TO REDUCE TREATMENT BURDEN

A three-cycle regimen of VEC chemotherapy may be a viable alternative to the standard six-cycle regimen for patients with HRF retinoblastoma, offering similar 5-year disease-free survival with shorter treatment duration, comparable toxicity, and lower cost.[4] Others have suggested a more tailored regimen would be ideal.[7]

Given the lack of prospective randomized clinical trials in such cases and the rarity of retinoblastoma, the ultimate need remains obscure.[6] However, it is worth considering that reducing the total treatment duration could potentially alleviate significant financial barriers that can lead to treatment abandonment and increased mortality. ■

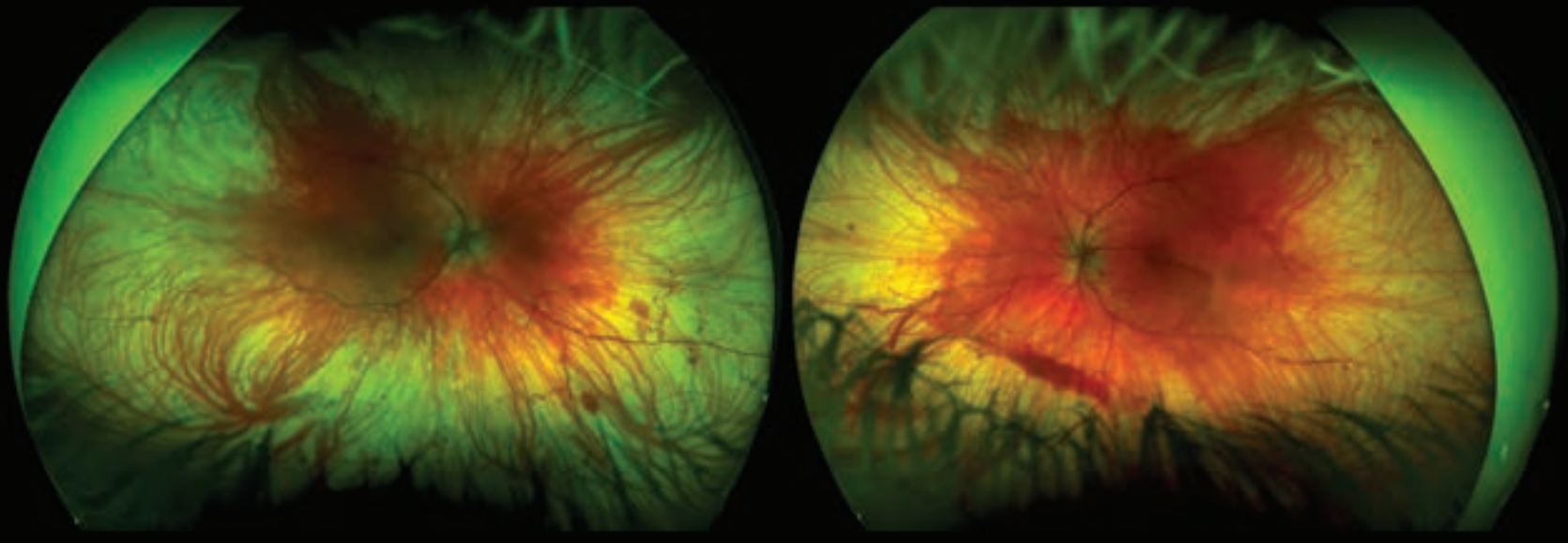
*Acknowledgement: Support provided in part by the Jerry A. Shields, MD, Eye Cancer Fund, Philadelphia, and the Eye Tumor Research Foundation, Philadelphia. The funders had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, and in the preparation, review, or approval of the manuscript. Carol L. Shields, MD, has had full access to all the data in the study and takes responsibility for the integrity of the data.*

1. Pandey AN. Retinoblastoma: an overview. *Saudi J Ophthalmol*. 2014;28(4):310-315.
2. Honavar SG, Singh AD, Shields CL, et al. Postenucleation adjuvant therapy in high-risk retinoblastoma. *Arch Ophthalmol*. 2002;120(7):923-931.
3. Kaliki S, Shields CL, Shah SU, et al. Postenucleation adjuvant chemotherapy with vincristine, etoposide, and carboplatin for the treatment of high-risk retinoblastoma. *Arch Ophthalmol*. 2011;129(11):1422-1427.
4. Ye H, Xue K, Zhang P, et al. Three vs 6 cycles of chemotherapy for high-risk retinoblastoma: a randomized clinical trial. *JAMA*. 2024;332(19):1634-1641.
5. Mallipatna A, Gallie BL, Chévez-Barrios P, et al. Retinoblastoma. In: Amin MB, Edge SB, Greene FL (Eds). *AJCC Cancer Staging Manual*. 8th ed. New York City, NY: Springer; 2017:819-831.
6. Leahey AM, Shah A, Shields CL. Three vs 6 cycles of adjuvant chemotherapy for retinoblastoma. *JAMA Ophthalmol*. 2024;142(12):1107-1108.
7. Chantada G. Three cycles of adjuvant chemotherapy for high risk retinoblastoma may be too much or not enough. *JAMA Ophthalmol*. 2024;142;(12):1107-1108.

**MADISON M. WOODS, BA**
- Medical Student, Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia
- madison.woods@students.jefferson.edu
- Financial disclosure: None

**ROBERT J. MEDINA, BA**
- Medical Student, Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia
- robert.medina@students.jefferson.edu
- Financial disclosure: None

**CAROL L. SHIELDS, MD**
- Director, Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia
- Editorial Advisory Board Member, *Retina Today*
- carolshields@gmail.com
- Financial disclosure: None



# PDR IN THE SETTING OF OCULOCUTANEOUS ALBINISM

FIGURE 1

Panretinal photocoagulation was sufficient to treat this patient's vitreous hemorrhage and extensive neovascularization.

BY JAMES DOSSETT, MD; CHRISTINE CLAVELL, MD; AND GHASSAN GHORAYEB, MD, MBA

A 17-year-old girl with a history of type 1 diabetes and oculocutaneous albinism presented with blurred vision in her left eye, noted after a recent episode of diabetic ketoacidosis requiring hospitalization. Her BCVA was 20/25 OD and counting fingers at 3 ft OS. Widefield pseudocolor fundus images demonstrated bilateral proliferative diabetic retinopathy with extensive neovascularization of the discs and elsewhere, severe dot-blot hemorrhages and microaneurysms, and marked venous beading. Mild optic disc edema was noted in her right eye, and a large preretinal hemorrhage was found in the inferior periphery of her left eye. Bilateral fundus hypopigmentation was also present, consistent with her history of albinism (Figure 1). Fundus autofluorescence further characterized the impressive extent of the bilateral neovascular proliferative disease (Figure 2).

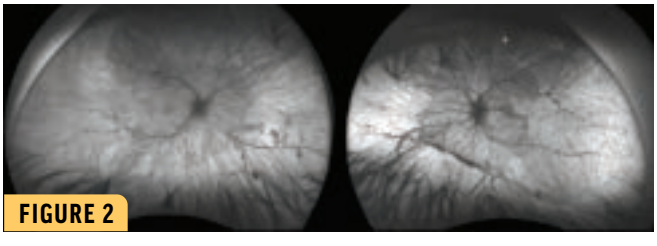


FIGURE 2

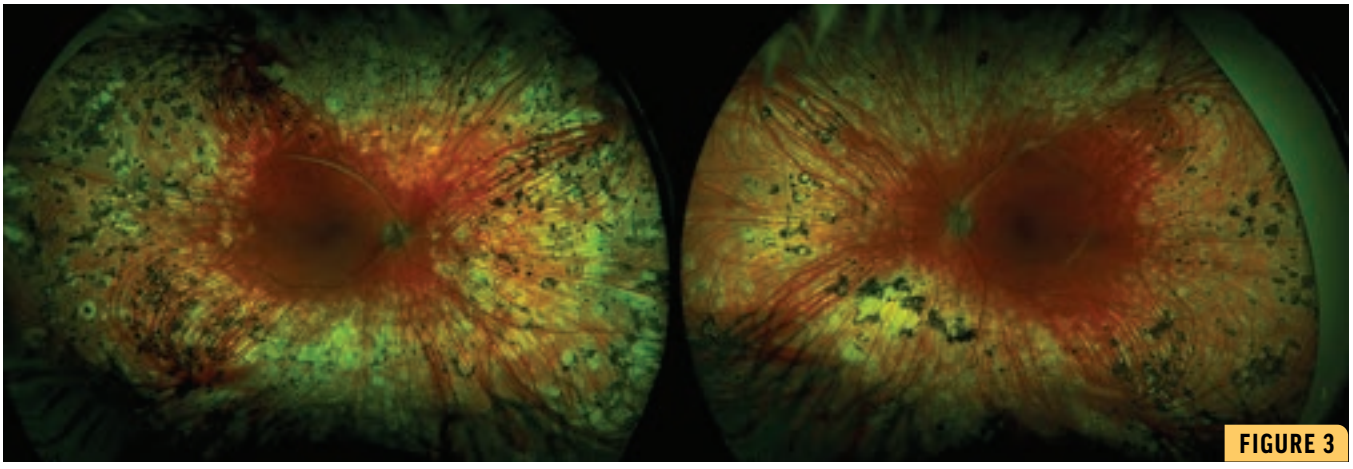


FIGURE 3

## TREATMENT APPROACH

The patient was unable to tolerate laser procedures in the clinic. Over the subsequent 9 months, she went to the OR three times for panretinal photocoagulation (PRP) in each eye under general anesthesia. Adequate laser uptake was obtained, despite retinal pigment epithelial hypopigmentation related to her history of albinism. The vitreous hemorrhage in her left eye improved, and the neovascularization regressed in each eye, solely from PRP without the need for supplemental intravitreal anti-VEGF injection.

At the final follow-up 3 years later, her VA had improved to 20/25 OD and 20/50 OS. Fundus photography demonstrated bilateral peripheral laser scarring 360° with complete regression of the neovascularization (Figure 3). ■

**JAMES DOSSETT, MD**
- Assistant Professor, University of New Mexico, Albuquerque, New Mexico
- jamespdossett@gmail.com
- Financial disclosure: None

**CHRISTINE CLAVELL, MD**
- Vitreoretinal Surgeon, Eye Associates of New Mexico, Albuquerque, New Mexico
- Financial disclosure: None

**GHASSAN GHORAYEB, MD, MBA**
- Vitreoretinal Surgery Fellowship Director, West Virginia University Eye Institute, Morgantown, West Virginia
- Financial disclosure: None

# INDEX OF ADVERTISERS



*This advertiser index is published as a convenience and not as part of the advertising contract. Although great care will be taken to index correctly, no allowances will be made for errors due to spelling, incorrect page number, or failure to insert.*

**SYFOVRE® (pegcetacoplan injection), for intravitreal use**
**BRIEF SUMMARY OF PRESCRIBING INFORMATION**
**Please see SYFOVRE full Prescribing Information for details.**

## INDICATIONS AND USAGE

SYFOVRE is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

## CONTRAINDICATIONS

**Ocular or Periocular Infections**
SYFOVRE is contraindicated in patients with ocular or periocular infections.
**Active Intraocular Inflammation**
SYFOVRE is contraindicated in patients with active intraocular inflammation.
**Hypersensitivity**
SYFOVRE is contraindicated in patients with hypersensitivity to pegcetacoplan or to any of the excipients in SYFOVRE. Systemic hypersensitivity reactions (e.g., anaphylaxis, rash, urticaria) have occurred.

## WARNINGS AND PRECAUTIONS

**Endophthalmitis and Retinal Detachments**
Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
**Retinal Vasculitis and/or Retinal Vascular Occlusion**
Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
**Neovascular AMD**
In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
**Intraocular Inflammation**
In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.
**Increased Intraocular Pressure**
Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

## ADVERSE REACTIONS

**Clinical Trials Experience**
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.
The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.
**Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY**

| Adverse Reactions | PM (N = 419) % | PEOM (N = 420) % | Sham Pooled (N = 417) % |
|---|---|---|---|
| Ocular discomfort* | 13 | 10 | 11 |
| Neovascular age-related macular degeneration* | 12 | 7 | 3 |
| Vitreous floaters | 10 | 7 | 1 |
| Conjunctival hemorrhage | 8 | 8 | 4 |
| Vitreous detachment | 4 | 6 | 3 |
| Retinal hemorrhage | 4 | 5 | 3 |
| Punctate keratitis* | 5 | 3 | <1 |
| Posterior capsule opacification | 4 | 4 | 3 |
| Intraocular inflammation* | 4 | 2 | <1 |
| Intraocular pressure increased | 2 | 3 | <1 |

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:
**Ocular discomfort** included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye
**Neovascular age-related macular degeneration** included: exudative age-related macular degeneration, choroidal neovascularization
**Punctate keratitis** included: punctate keratitis, keratitis
**Intraocular inflammation** included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic ischemic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

**Postmarketing Experience**
The following adverse reactions have been identified during postapproval use of SYFOVRE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Eye disorders: retinal vasculitis with or without retinal vascular occlusion. Systemic reactions: anaphylaxis, rash, and urticaria.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**
Risk Summary
There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.
Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
**Lactation**
Risk Summary
It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.
**Females and Males of Reproductive Potential**
Contraception
*Females*: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.
**Pediatric Use**
The safety and effectiveness of SYFOVRE in pediatric patients have not been established.
**Geriatric Use**
In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

## PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing endophthalmitis, retinal detachments, retinal vasculitis with or without retinal vascular occlusion and neovascular AMD. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist. Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured for:
Apellis Pharmaceuticals, Inc.
100 Fifth Avenue
Waltham, MA 02451

SYF-PI-20Dec2024-3.0



12/24 US-PEGGA-2400436 v1.0

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

# Save more retinal tissue

Through Year 2, in OAKS and DERBY, SYFOVRE slowed GA lesion growth vs sham pooled.[1]

SYFOVRE slowed GA lesion growth with **increasing effects over time up to 42%** in Year 3 (GALE) vs projected sham in patients without subfoveal lesions[1,2]

- Through Year 2 (OAKS and DERBY), SYFOVRE slowed GA lesion growth ($mm^2$) vs sham pooled by 22% (3.11 vs 3.98) and 18% (3.28 vs 4.00) monthly, and by 18% (3.26 vs 3.98) and 17% (3.31 vs 4.00) EOM[1,2]
- Through Year 3 (GALE), SYFOVRE slowed GA lesion growth ($mm^2$) vs sham pooled/projected sham by 25% (4.46 vs 5.94) monthly and 20% (4.74 vs 5.94) EOM. The greatest differences were observed in Year 3[2]
  - Reductions in patients without subfoveal lesions at baseline through Year 3: 32% (5.10 vs 7.54 (n=95)) monthly and 26% (5.60 vs 7.54 (n=104)) EOM. In this subset of patients, there was a 42% reduction with monthly SYFOVRE in Year 3 vs projected sham

SE in trials (monthly, EOM, sham pooled/projected sham): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17; GALE (total population): 0.16, 0.16, 0.19; GALE (without subfoveal): 0.26, 0.31, 0.41[1,2]

EOM=every other month; GA=geographic atrophy; SE=standard error.

**GALE Trial Limitations:** GALE is an ongoing open-label, multi-center extension study, subject to patient dropouts over time. The analysis for the first year of GALE utilized a projected sham and may not reflect rate of change of all patients with GA. Projected sham assumes linear growth rate from Months 24-36 (GALE Year 1) based on the average of the mean rate of change of each 6-month period of sham treatment in OAKS and DERBY and natural history studies, which have shown there is a high correlation between prior 2-year growth rates of GA lesions and subsequent 2-year growth rates. This is a prespecified analysis but there is no statistical testing hierarchy, therefore the results on the individual components need cautious interpretation. Open-label studies can allow for selection bias.[2,3]

**Discover more at SyfovreECP.com**

## INDICATION

SYFOVRE® (pegcetacoplan injection) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, in patients with active intraocular inflammation, and in patients with hypersensitivity to pegcetacoplan or any of the excipients in SYFOVRE. Systemic hypersensitivity reactions (e.g., anaphylaxis, rash, urticaria) have occurred.

### WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- **Retinal Vasculitis and/or Retinal Vascular Occlusion**
  - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.
- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

### ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

**Please see Brief Summary of Prescribing Information for SYFOVRE on the adjacent page.**

**OAKS and DERBY Trial Design:** SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 2-year, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration) with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE every other month, sham monthly, or sham every other month, for 2 years. Change from baseline in the total area of GA lesions in the study eye ($mm^2$) was measured by fundus autofluorescence (FAF).[1,2]

**GALE Trial Design:** GALE (N=790) is a multi-center, 3-year, Phase 3, open-label extension study to evaluate the long-term safety and efficacy of pegcetacoplan in subjects with geographic atrophy secondary to age-related macular degeneration. Patients enrolled in GALE include those who completed OAKS or DERBY after 2 years and 10 patients from Phase 1b Study 103. Patients with GA (atrophic nonexudative age related macular degeneration) with or without subfoveal involvement, secondary to AMD were assigned to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly or SYFOVRE EOM for 3 years. The first visit was required to be within 60 days of the final visit in OAKS and DERBY.[2]

**References: 1.** SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2024. **2.** Data on file. Apellis Pharmaceuticals, Inc. **3.** Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology*. 2007;114(2):271–277. doi:10.1016/j.ophtha.2006.09.016.

Apellis