

A PUBLICATION BY

REVIEW
OF OPHTHALMOLOGY

RETINA[®] SPECIALIST

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Chuck is a real patient with GA, and Dr. Esther Kim is his retina specialist who treats his GA with IZERVAY.

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**Chuck loves to play bridge—
Dr. Kim loves to keep him in the game for longer.**

Treat GA early with IZERVAY to protect healthy retinal cells for longer^{1,2*}

Scan to explore IZERVAY: The #1 prescribed FDA-approved treatment for new GA patients^{3†}



izervay
(avacincaptad pegol
intravitreal solution) 2 mg

Physicians and patients featured have been compensated.

*In 2 clinical trials of 624 people, IZERVAY was proven to reduce the annualized rate of GA lesion growth by 18%-35% in 1 year compared to those who were not treated.

†Based on Symphony data from 3/24-12/25. May not represent entire patient population.

INDICATION

IZERVAY® (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

IZERVAY is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

- Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

Neovascular AMD

- In the GATHER1 and GATHER2 clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization

(7% when administered monthly and 4% in the sham group) by Month 12. Over 24 months, the rate of neovascular (wet) AMD or choroidal neovascularization in the GATHER2 trial was 12% in the IZERVAY group and 9% in the sham group. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

Increase in Intraocular Pressure

- Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$ and occurred with frequency $\geq 2\%$ vs. sham) reported in patients receiving IZERVAY for up to 24 months in GATHER2: conjunctival hemorrhage, blurred vision, increased IOP, wet AMD, punctate keratitis, and eye pain.

Please see Brief Summary of Full Prescribing Information on adjacent page.

References: 1. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079-1091. 2. IZERVAY. Package insert. Northbrook, IL: Astellas Pharma US, Inc.; 2026. 3. Astellas Pharma US, Inc. IZERVAY. Data on File.

IZERVAY® (avacincaptad pegol intravitreal solution)

Rx only

Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 800-707-4479.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage

The recommended dosage for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

IZERVAY is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

IZERVAY is contraindicated in patients with active intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

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5.2 Neovascular AMD

In the GATHER1 and GATHER2 clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12.

Over 24 months, the rate of neovascular (wet) AMD or choroidal neovascularization in the GATHER2 trial was 12% in the IZERVAY group and 9% in the sham group. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Ocular and periocular infections
- Active intraocular inflammation
- Endophthalmitis and retinal detachments
- Neovascular AMD
- Increase in intraocular pressure

6.1 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.

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY for up to 12 months pooled across the GATHER1 and GATHER2 studies are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye up to 12 months

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Blurred Vision*	8%	5%
Choroidal neovascularization	7%	4%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

Adverse reactions reported in ≥ 2% of patients who received treatment with IZERVAY for up to 24 months in the GATHER2 study are listed below in Table 2.

Table 2: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye up to 24 months

Adverse Drug Reaction	IZERVAY N=225	Sham N=222
Conjunctival hemorrhage	17%	9%
Blurred vision ¹	14%	5%
Increased IOP	13%	1%
Choroidal neovascularization	12%	9%
Punctate keratitis ²	10%	8%
Eye pain	7%	4%
Retinal hemorrhage	4%	3%
Vitreous floaters	4%	<1%
Ocular hypertension	4%	0
Blepharitis	3%	<1%
Corneal abrasion	2%	<1%

¹ Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently and blindness transient.

² Punctate keratitis includes punctate keratitis and keratitis.

Photopsia, optic ischemic neuropathy, vitreous hemorrhage, vitreal cells, vitritis, and endophthalmitis were each reported in ≤ 1% of patients treated with IZERVAY for up to 24 months across the GATHER1 and GATHER2 studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary

There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.5 times and 3.4 times the human exposure, respectively, based on Area Under the Curve (AUC), following a single 2 mg intravitreal (IVT) dose (see Animal Data).

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.

Animal Data

An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily IV injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.5 times the human AUC of 999 ng•day/mL (23976 ng•hr/mL) following a single 2 mg IVT dose. An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.4 times the human AUC of 999 ng•day/mL (23976 ng•hr/mL) following a single 2 mg IVT dose.

8.2 Lactation

There is no information regarding the presence of avacincaptad pegol in human milk, or the effects of the drug on the breastfed infant or on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

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

8.4 Pediatric Use

Safety and effectiveness of IZERVAY in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

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Risking The Disc

Going from bench to bedside is an incredibly long process with many regulatory hurdles, all intended to ensure safety and efficacy of new therapeutics before they are widely adopted in medicine. In the retina space, it probably wasn't until brolucizumab that many of us realized clinical trial safety data doesn't always translate into broader patient safety once you go from hundreds of patients being treated in trials to many thousands in the real world. We've seen this repeated to some extent with the complement inhibitors and their (fortunately rarer) occurrence of occlusive retinal vasculitis compared to brolucizumab.

At the recent Retina Society meeting in Los Angeles, our colleague Dr. David Brown gave a striking presentation on the association between anti-complement therapy and thickening of the peripapillary retinal nerve fiber layer.

First off, I have to give him kudos for actually getting peripapillary RNFL scans on so many patients for so long, as it's something that I rarely order. During his presentation, he reported performing serial RNFL scans on treatment naïve eyes, anti-VEGF injected eyes, and anti-complement injected eyes (both pegcetacoplan and avacincaptad pegol).

The treatment naïve and anti-VEGF treated eyes had a slight annual decrease in thickening as would be expected for aging, while the anti-complement treated eyes had an annual 4

to 5 μ m increase. He hypothesized that this isn't a neuroprotective reversal of RNFL loss but rather a thickening of the existing RNFL.

So what's the big deal? There appears to be a <1-percent risk of acute ischemic optic neuropathy in patients receiving anti-complement inhibitors based on data from the pivotal trials. This progressive RNFL thickening may be a mechanism similar to how a crowded optic disc with a small cup is considered a "disc at risk" for non-arteritic ischemic optic neuropathies. Dave showed a striking example where you could see progressive, dramatic shrinking of the cup on serial imaging.

I walked away with a couple of take-home messages: 1) In patients receiving anti-complement injections, it may be worthwhile to obtain peripapillary RNFL thickness measurements, with a plan to hold injections if there is a noticeable increase above the normative threshold. 2) Use caution in treating patients who already have a small cup-to-disc ratio <0.2 as RNFL thickening in these eyes may be more likely to choke the disc. ^{RS}

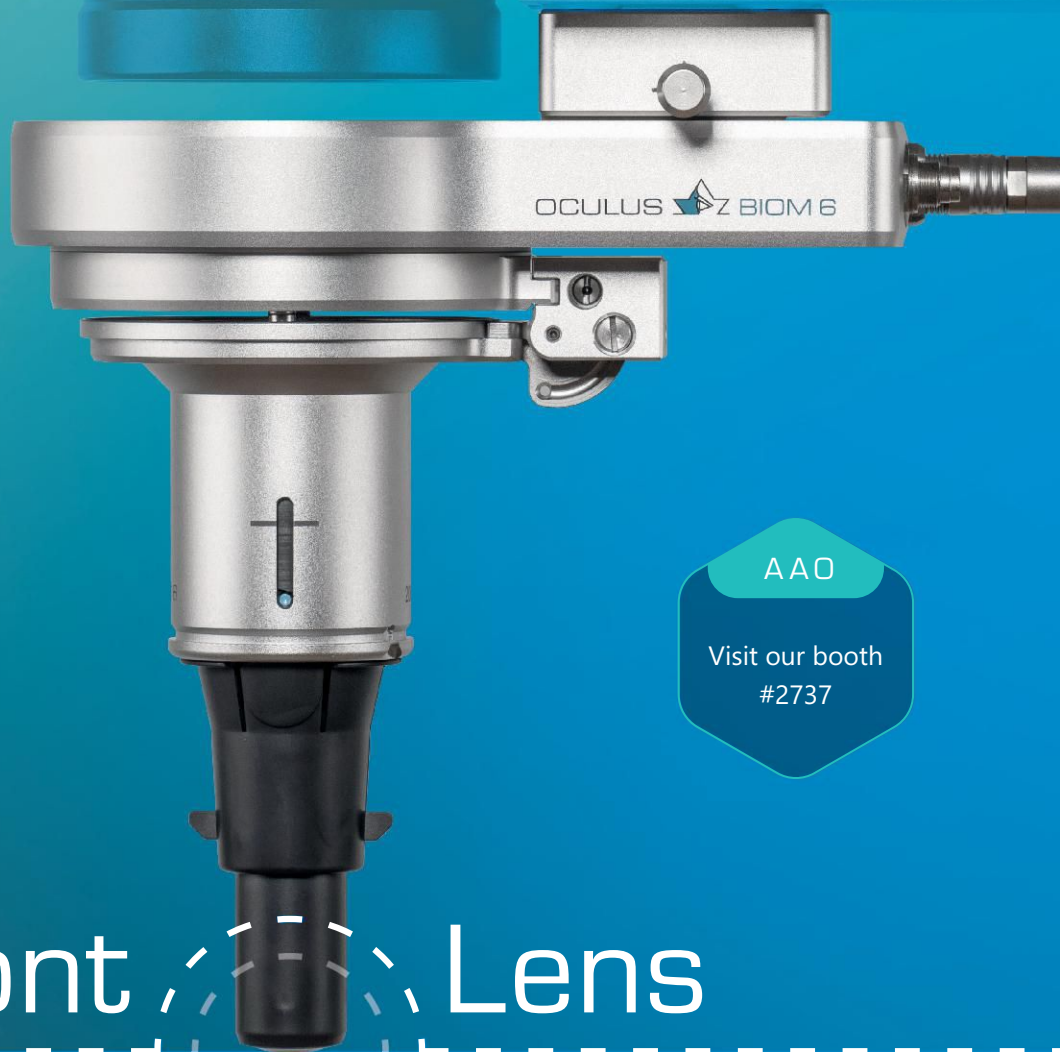


Flanary WE, et al/everounds.org²

1. Brown, DM (2026, September 25). Anti-Complement Therapy Induced Thickening of the Retinal Nerve Fiber Layer: A Longitudinal Analysis [Paper presentation]. 59th Annual Meeting of The Retina Society, Los Angeles, CA.

2. Image: Flanary WE, Phillips D, Kardon RH. Posterior ischemic optic neuropathy. April 3, 2015; Available from: <https://everounds.org/cases/212-PION.htm>. Used under Creative Commons License: <https://creativecommons.org/licenses/by-nc-nd/3.0/>.

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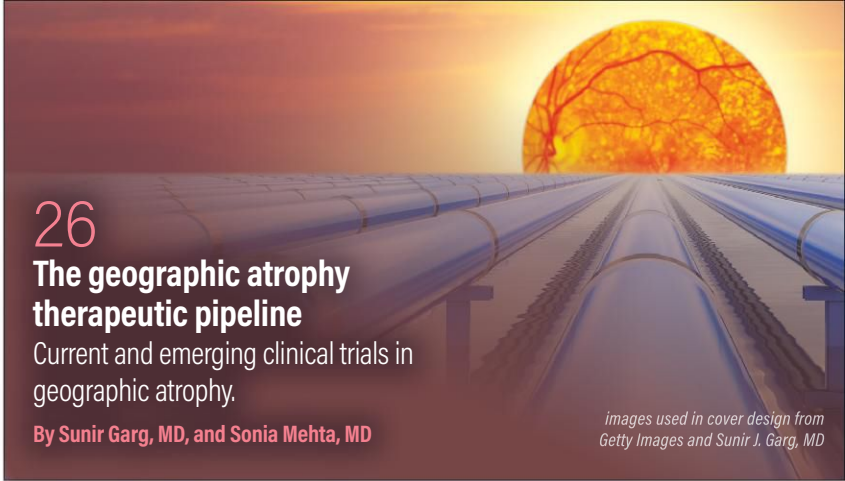
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*images used in cover design from
Getty Images and Sunir J. Garg, MD*

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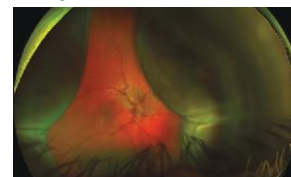
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When a clinical trial becomes something to bet on

By Jayanth Sridhar, MD

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



Harness the tech with the survival effect ON PHOTORECEPTORS¹



See the data behind ENCELTO

Scan the QR code or visit
ENCCELTO.com/ecp

INDICATIONS AND USAGE

ENCCELTO 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

ENCCELTO 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

ENCCELTO 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 an 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 ($\geq 2\%$) 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

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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)

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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.

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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 $\geq 2\%$ patients and with higher frequency in ENCELTO group compared to Sham group in Study 1 and Study 2.

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

Adverse Reactions	ENCELTO	Sham
	(N=117)	(N=111)
	n (%)	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.

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A review of uveal effusion syndrome

A discussion of the clinical spectrum, imaging and a subtype-driven approach to management.

By **Justin C. Muste, MD**
and **Jordan D. Deaner, MD**



Justin C. Muste, MD



Jordan D. Deaner, MD

A 72-year-old male was referred for bilateral panuveitis and posterior scleritis complicated by serous retinal detachments. Past ocular history was notable for bilateral phacoemulsification and intraocular lens implantation. His past medical history included hypertension, gout and gastroesophageal reflux disease. Past medical history was most remarkable for a history of bilateral panuveitis diagnosed two years prior to presentation secondary to syphilis. The patient had previously completed two weeks of intravenous penicillin G treatment at the time of initial diagnosis. Since that time, he was continually on oral prednisone (variable dosing, but as high as 60 mg per day). He was referred for a worsening recurrence of posterior scleritis—initially presenting in the left eye and developing in the right eye four weeks later—now representing a severe bilateral exacerbation.

On presentation, the patient was maintained on 60 mg of prednisone daily and complained only of blurred vision and had never had ocular pain. He was counting fingers in both eyes. Intraocular pressure was 15 mmHg in the right eye and 18 mmHg in the left eye. The patient endorsed no ocular pain on his current dose of 60 mg of oral prednisone. The anterior segment examination disclosed no cells with well-positioned intraocular lenses in both eyes. The posterior segment examination was notable for a rare vitreous cell with both serous choroidal and retinal detachments in both eyes (*Figure 1*).

A differential diagnosis was created for a patient with serous retinal and choroidal detachments, and includes broadly inflammatory, infectious, neoplastic/infiltrative, vascular and structural causes:

- Inflammatory
 - Vogt–Koyanagi–Harada (VKH)
 - posterior scleritis

- sympathetic ophthalmia
- Infectious
 - endogenous endophthalmitis
 - syphilis
- Choroidal neoplastic/infiltrative disease
 - choroidal melanoma
 - choroidal metastasis
 - choroidal lymphoma
 - choroidal hemangioma
 - paraneoplastic syndromes
- Vascular
 - severe hypertensive retinopathy and choroidopathy
 - preeclampsia/eclampsia
 - bullous central serous chorioretinopathy
- Structural
 - hypotony
 - drug-associated ciliochoroidal effusion
 - trauma
 - glaucoma surgery or intraocular surgery
 - laser photocoagulation
- Medication
 - sulfa drugs
 - mefenamic acid
 - phendimetrazine tartrate
 - bupropion
 - ephedrine
 - topiramate

B-scan ultrasonography confirmed serous choroidal detachments, inferior serous retinal detachments, and didn't show evidence of any intraocular mass lesions, T-sign or retrobulbar hypoechoic lesions. A-scan ultrasonography revealed an axial length of 22.31 mm in the right eye and 22.54 mm in the left eye. Fluorescein angiography was deferred due to previously documented fluorescein allergy. Indocyanine green angiography showed evidence of early choroidal vascular tortuosity and congestion with diffuse late hyperfluores-

BIOS

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Dr. Deaner is on the retina service at Wills Eye/Mid-Atlantic Retina. He is an assistant professor of ophthalmology at the Sidney Kimmel Medical College of Thomas Jefferson University in Philadelphia, and is on the faculty of the Vickie and Jack Farber Vision Research Center in Philadelphia.

Conflicts of Interest:

Dr. Deaner reports the following unrelated to the submitted work: He's a consultant for Abbvie, Genentech and Regeneron. He's on the speakers bureau and consults for ANI and Bausch + Lomb.

Dr. Muste reports no conflicts of interest.

cence without evidence of a choroidal vascular lesion, hot spots or hypofluorescent choroidal lesions. Prior laboratory work-up from the referring doctor was reviewed and showed a positive FTA-Abs, with a low RPR titer of 1:2. His RPR titer was repeated following intravenous penicillin therapy and remained stable at 1:2. Additional testing from the referring doctor disclosed the following:

- negative Lyme antibodies;
- HIV testing;
- QuantiFERON gold;
- angiotensin-converting enzyme;
- rheumatoid factor;
- C-reactive protein;
- erythrocyte sedimentation rate;
- human leukocyte antigen-B27;
- antinuclear antibody;
- antineutrophil cytoplasmic antibody testing
- an unremarkable complete metabolic panel;
- complete blood counts; and
- chest X-Ray.

Blood pressure was checked in office and the patient was normotensive. His medication list was thoroughly reviewed, and no offending agents were identified.

Given the patient's chronic presentation without ocular pain and the absence of evidence of intraocular inflammation or infection, intraocular neoplasm, hypotony or a drug-associated adverse effect, as well as well-controlled hypertension and appropriately treated syphilis, a tentative diagnosis of uveal effusion syndrome was made by exclusion. However, his serous choroidal and retinal detachments persisted on high-dose steroids.

The decision was made to initiate a taper of oral steroids by 10 mg a week and proceed with four scleral windows with sclerostomies in the right eye, and, if successful, proceed in the left eye (*See surgical video at <https://bit.ly/4ySzqg8>*). Intraoperatively, his sclera was noted to be abnormally thickened and spongiform OU. His postoperative course was unremarkable,

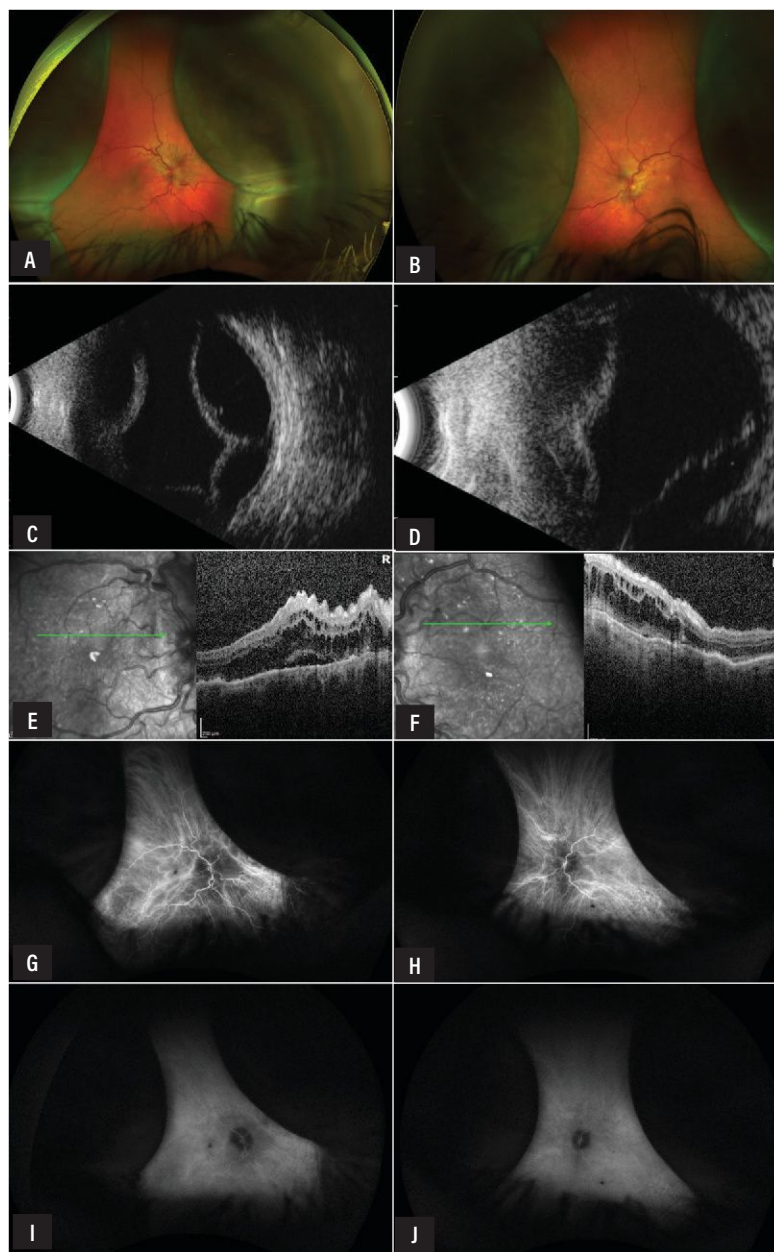


Figure 1. Color fundus photos showing prominent serous choroidal detachments with shallow serous retinal detachments in the right eye (A) and left eye (B). B-scan ultrasonography confirmed both serous choroidal detachment in the right eye (C) and serous choroidal and retinal detachment in the left eye (D). Horizontal rasters on optical coherence tomography of the right eye (E) and left eye (F) revealed RPE changes, a thickened choroid, macular edema and small pockets of subretinal fluid. Early indocyanine green angiography of both eyes revealed increased tortuosity of the choroidal vessels of the right eye (G) and left eye (H) that transitioned to later diffuse hyperfluorescence in both right (I) and left (J) eyes.

with the choroidal detachment resolving at one week after surgery and the serous detachments resolving at one month in both eyes. At his final postoperative visit nearly 11 months after scleral window, the vision improved to 20/100 in the right eye and remained stable at CF in the left. His examination showed demarcation lines and diffuse pigment mottling; however, no serous retinal detachment was appreciated (See Figure 2).

Discussion

Uveal effusion syndrome is a rare, frequently bilateral disorder best understood as the abnormal accumulation of protein-rich fluid within the suprachoroidal and supraciliary spaces, which generates serous detachment of the choroid and ciliary body, and subsequently the retina. Because choroidal melanoma, metastasis, posterior scleritis, VKH disease, and central serous chorioretinopathy can each

reproduce elements of the picture, UES is fundamentally a diagnosis of exclusion.^{1,2} This article reviews the pathophysiology, presentation, diagnosis and treatment of UES.

Pathophysiology

In brief, UES can be summarized as an abnormal collection of fluid that expands the suprachoroidal space, elevating the choroid and ciliary body and secondarily detaching the overlying neurosensory retina.³⁻⁵ The histopathology of resected sclera in affected eyes shows disorganized collagen fiber bundles and deposition of glycosaminoglycans and proteoglycans within the extracellular matrix.^{2,4} This abnormal, thickened sclera resists the normal transscleral egress of albumin and other macromolecules from the suprachoroidal space. These retained oncologically active proteins then attract and retain fluid. Accordingly, Osaka, Japan's Masanobu Uyama, MD, proposed a framework for better understanding causes of UES (See Table 1).

As discussed below, the distinction has a role in treatment. Types 1 and 2 share the scleral pathology that scleral surgery is designed to address. Type 3 eyes may be better treated by initial medical therapy.^{2,4,6}

Presentation

UES classically affects otherwise healthy middle-aged, hypermetropic men.¹ One eye may become symptomatic months to years before the fellow eye follows. Involvement is bilateral in roughly two-thirds of patients. Patients present with painless (89 percent) blurring or metamorphopsia as subretinal fluid tracks into the macula.⁷ Patients may give a history of relapsing-remitting vision loss with spontaneous exacerbations and partial remissions that can span years.

Examination discloses bullous, non-rhegmatogenous retinal detachment with characteristic shifting fluid. It's possible that annular ciliochoroidal detachment and dilated episcleral vessels may also be present. Though a small number of vitreous cells

Table 1. Uveal Effusion Syndrome Classification and Findings^{2,6}

	Type 1 Uveal Effusion (nanophthalmic)	Type 2 Uveal Effusion (non-nanophthalmic)	Type 3 Uveal Effusion (non-nanophthalmic)
Anterior Segment	- Minimal to no cell - Blood in Schlemm's canal - Dilated episcleral vessels	- Minimal to no cell	- Minimal to no cell
Posterior Segment	- Ciliochoroidal detachment/elevation - Subretinal fluid - Retinal folds - Leopard spot changes in RPE - Optic nerve swelling - Mild to moderate vitreous cells		
Axial length	Short axial length (<20.5 mm)	Normal or slightly short axial length (> 20 mm)	Normal or slightly short axial length (> 20 mm)
Refractive error	Hypermetropic	Non-hypermetropic	Non-hypermetropic
Sclera	Thickened/abnormal	Thickened/abnormal	Normal
Treatment	Surgery effective	Surgery favorable	Medical treatment favorable

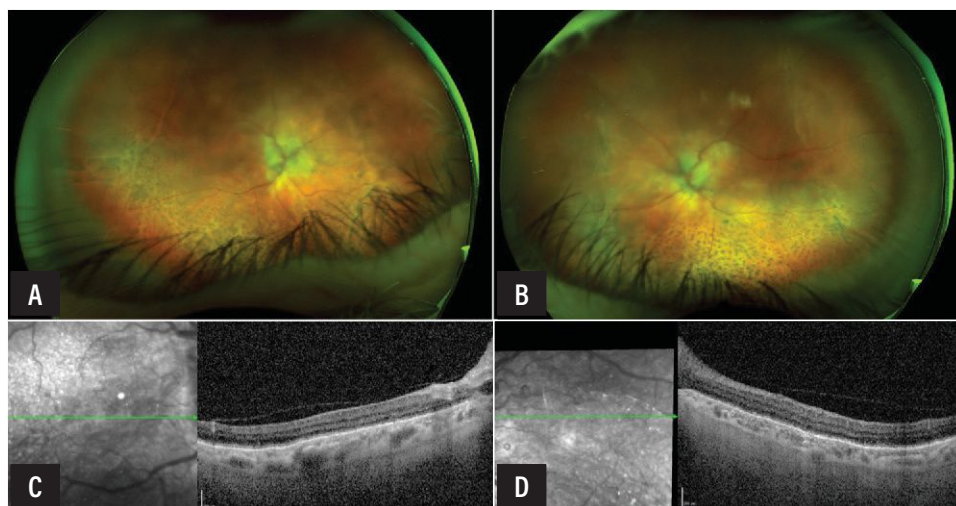


Figure 2. Color fundus photograph of the right eye (A) and left eye (B) demonstrating resolution of the serous retinal and choroidal detachments with subsequent demarcation lines and diffuse pigment mottling. Optical coherence tomography of the right eye (C) and left eye (D) revealing resolution of the subretinal fluid and macular edema.

may be present, there's no robust inflammatory reaction in the posterior or anterior chamber. Intraocular pressure is typically normal. However, in the nanophthalmic eye, a short axial length and crowded anterior segment predispose to secondary angle closure; in these patients, acute or chronic angle-closure glaucoma may precede recognition of the effusion.^{7,8}

Diagnostic features

UES remains a diagnosis of exclusion. The first task is to rule out the conditions it imitates: primary choroidal neoplasms and metastasis; posterior scleritis; VKH disease; choroiditis; CSCR; hypotony; drug related adverse effects; hypertensive retinopathy; and choroidopathy. A careful history, ocular examination, lab work, and multimodal imaging can aid to that end.

As part of a complete ocular examination, emphasis should be placed on searching for cell and retinal breaks that would suggest other etiologies. Over time, chronic subretinal fluid produces the characteristic "leopard-spot" pattern of the retinal pigment epithelium: scattered, mottled yellow-orange deposits that are a secondary consequence of long-standing detachment rather than an acute sign. Because they

develop only after the fluid has been present for some months, their absence early doesn't exclude the diagnosis, and their persistence after resolution shouldn't be mistaken for active disease.^{6,7}

Multimodal imaging both supports the diagnosis and helps to exclude mimics. B-scan ultrasonography demonstrates the combination of choroidal and retinal detachment, frequently as an extended, multilayered and kinetically mobile detachment, and can show scleral thickening.⁹ Simultaneously B-scan excludes a choroidal mass and identifies the "T-sign" that signals posterior scleritis. Additionally, an A-scan supplies the accurate axial length needed to identify nanophthalmos. Ultrasound biomicroscopy can reveal an annular peripheral ciliochoroidal detachment and a characteristically spongy, edematous ciliary body, sometimes with interstitial lacunae.⁹

Fundus autofluorescence will show mixed hyper- and hypoautofluorescent pattern. Fluorescein angiography highlights the "leopard spots" as a mottled pattern of hyper- and hypofluorescence corresponding to the RPE changes. Crucially, it'll confirm the absence of pinpoint or expansile leakage that defines CSCR.^{6,7} Indocyanine green angiography shows diffuse granular

choroidal hyperfluorescence, most evident in the early phase, in keeping with a generalized choroidal process rather than a focal leak. Optical coherence tomography can appreciate subretinal fluid, RPE undulations or folds and increased choroidal thickness, and is useful for tracking the macula through treatment.

Auxiliary lab work can help ensure there's no underlying infectious disease with protean manifestations, particularly tuberculosis or syphilis. A CT or MRI can provide a further check against an occult mass. In certain instances, MRI (T1) with gadolinium can show uveal detachment.⁷ Though less generalizable, clinicians may consider genetic testing in the nanophthalmic (Type 1) subtype. Five genes (i.e., *MFRP*, *TMEM98*, *PRSS56*, *BEST1* and *CRB1*) and two loci have been implicated in familial forms of nanophthalmos.¹⁰ Knowledge of this inheritance pattern can facilitate genetic counseling for familial forms of this condition and may help to decrease amblyopia from uncorrected hyperopia, heighten monitoring and prevent vision loss from complications.

Treatment

Management is individualized and guided by Uyama subtype, disease severity and symptomatic impact. As illustrated in the case presented here, Type 2 eyes benefit from quadrant partial-thickness scleral windows placed anterior to the equator.^{4,5} Type 1 eyes also benefit from this intervention. Vortex vein decompression is an alternative but carries a higher risk of vein amputation and hemorrhage, and most surgeons favor sclerectomy.^{3,5,11} The anatomic results in these subtypes are good. Recent series and a systematic review confirm high reattachment rates with quadrant lamellar sclerectomy and sclerostomy, alongside meaningful visual recovery.¹²

Type 3 eyes may be better approached with an initial medical therapy. In the largest reported experience, Wills Eye Hospital's Carol Shields, MD, and colleagues managed 104 eyes with corticosteroids de-

livered by oral, periocular or topical routes, or with observation; using these approaches, disease control was achieved in the large majority, and scleral window surgery was required in only about 5 percent, with some eyes resolving spontaneously.⁷

Additional considerations for management include high risk of angle-closure glaucoma from anterior-segment crowding that may require referral or management by cataract extraction or laser peripheral iridotomy. Finally, given the relapsing course and frequent bilaterality, long-term follow-up is essential.

Conclusion

Uveal effusion syndrome is a diagnosis of exclusion best evaluated using a variety of tools at the retina specialist's disposal. B-scan ultrasonography aids diagnosis and, together with angiography, helps distinguish UES from possible mimics. Eyes with nanophthalmos or abnormal sclera (types 1 and 2, respectively) are generally best approached with scleral surgery, while eyes with a normal sclera (type 3) more often respond to corticosteroids. 

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Traumatic phacocoele

Addressing a complex case of phacocoele by highlighting key considerations for its surgical approach.

Post-traumatic dislocation of the crystalline lens into the subconjunctival space, referred to as phacocoele, is a rare occurrence caused by an indirect scleral rupture of the globe. Cases of perforation due to ocular trauma are considered ophthalmic emergencies, requiring immediate and meticulous management.¹ The presence of significant subconjunctival hemorrhage and hypotonia should raise suspicion for an occult perforation. B-scan ultrasonography is crucial for diagnosis, particularly in cases involving hyphema or vitreous hemorrhage. The absence of lens echoes on the scan is notable, and it also helps in identifying vitreous hemorrhages, retinal detachments, suprachoroidal hemorrhages and endophthalmitis.²

This report provides detailed insights into a case of phacocoele and its outcome, while also addressing an important consideration in this condition, which is primary versus secondary intraocular lens implantation.

Surgical management

This patient presented to our clinic 10 days after being struck in the right eye by an iron bar, reporting pain and vision loss (limited to light perception). A slit-lamp exam revealed a solid, globular yellowish mass in the subconjunctival space in the su-



Figure 1. External photography of the right eye, highlighting the boundaries of the subconjunctival mass.

View the Video

Go to <https://vimeo.com/1229305603> or scan the QR code.



peronasal quadrant, with a smooth surface and rounded margins. Visualization of the anterior chamber was obstructed by corneal edema and a 3.5-mm hyphema. Aphakia and iris atrophy from 10 to 1 o'clock were noted, with an intraocular pressure of 17 mmHg and no relative afferent pupillary defect. B-scan ultrasonography showed dispersed hemorrhage in the anterior vitreous and the absence of a lens spike, confirming the diagnosis of traumatic phacocoele.

Explorative surgery was performed under retrobulbar anesthesia. A 360° conjunctival peritomy was conducted, and the lens with its intact capsule was removed from the

subconjunctival space. A 7-mm superior scleral wound with uveal tissue remnants was observed. Although a human scleral graft was prepared, it wasn't needed due to the regular and linear nature of the wound. A standard three-port pars plana vitrectomy was

Gabriel Castillo Sandoval Barbosa, MD



Gabriel Castillo Sandoval Barbosa, MD

BIO

Dr. Barbosa is a Brazilian ophthalmologist specializing in cataract and retina. He's currently a professor at Instituto Suel Abujamra, São Paulo.

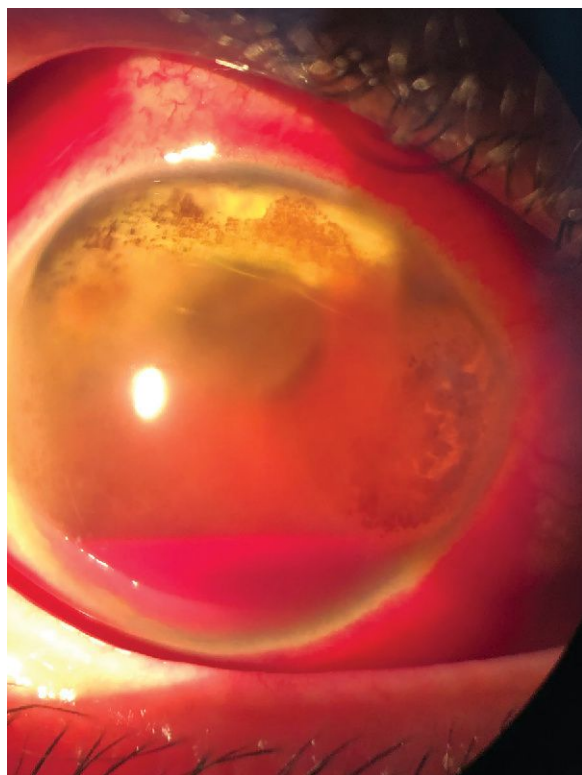


Figure 2. Slit-lamp examination showing corneal edema, hyphema of 3.5 mm height, aphakia and iris atrophy from 10 o'clock to 1 o'clock.

then performed, followed by scleral introflexion to alleviate potential residual tractions at the wound site. During the vitrectomy, multiple areas of scar fibrosis with hyperpigmented, well-defined grayish lesions were identified along the retina. The eye was left aphakic to allow for better surgical preparation in a subsequent procedure. At the one-month follow-up, the best-corrected visual acuity of the right eye was 20/60.

lens near the scleral wound, followed by exploration of the injury. The scleral rupture should be repaired, and partial vitrectomy performed if needed. Scleral introflexion is advised to alleviate any residual traction, given the complexity of treating the vitreous base in these cases. IOL implantation can be deferred to a later session based on the condition of the eye.

One paper found that primary IOL implantation, using biometry from the non-traumatized contralateral eye to calculate IOL power, could lead to a significant refractive error of up to 4 D. However, after revising the approach and performing IOL exchange surgery using simulated keratometry and axial length measurements from the injured eye, the patient achieved emmetropia with a BCVA of 20/20.⁸ On the other hand, another report emphasized that using the biometry of the injured eye after primary repair of the globe was more accurate than using biometry of the non-traumatic eye to determine the IOL power with refraction deviation of only 1 D in secondary IOL implantation.⁹ Further, timely and effective intervention can ensure good visual recovery.

In the case reported here, the primary objective of the surgery was to preserve the integrity of the globe, allowing for a future procedure with optimized IOL power calculation under the best possible conditions. **RS**

Case takeaways

The most frequent location for a phacocoele is the superonasal quadrant near the limbus, attributed to the energy projection from an impact in the temporal region. The superotemporal area is the second most common site. Scleral ruptures typically occur between the limbus and the spiral of Tillaux.^{3,4} Phacocoele is more commonly observed in elderly individuals with a rigid sclera compared to children, who have more elastic ocular tissues. These cases are often accompanied by vitreous hemorrhage and retinal detachments.^{5,6}

The main objective in managing a phacocoele is to remove the displaced lens while preserving the integrity of the globe.⁷ In surgical management, it's recommended to first place the infusion port to prevent eye collapse during manipulation of the

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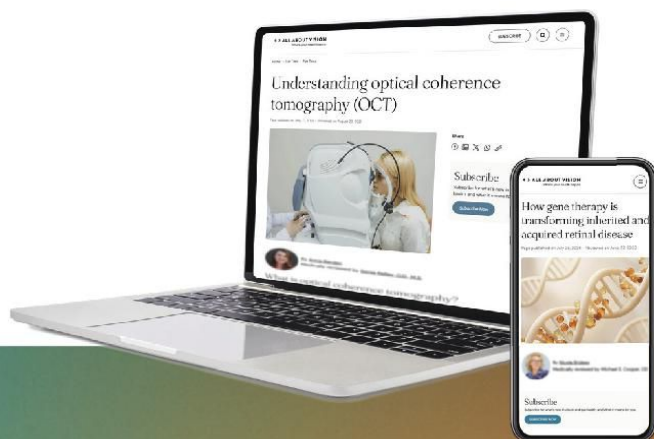
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When a clinical trial becomes something to bet on

Medicine (and retina, by proxy) may have just acquired a new kind of conflict of interest.

By Jayanth Sridhar, MD



Prediction platforms Kalshi and Polymarket now offer markets tied to FDA approvals and drug development.^{1,2} Kalshi recently announced a pilot program allowing people to trade on whether selected late-stage clinical trials will meet their primary endpoints. Kalshi says these markets will only open after enrollment is complete and prohibits trading by individuals with material nonpublic information. But beyond the regulatory questions lies a more uncomfortable issue for medicine: What happens when the outcome of a clinical trial becomes something people can directly bet on and the physicians closest to that trial are simultaneously posting, speaking and interacting publicly online?

Financial speculation around clinical research is hardly new. Pharmaceutical stocks can rise or fall dramatically after a trial result or FDA decision, and sophisticated investors have always tried to anticipate those outcomes. Prediction markets make the relationship much more explicit. Instead of investing in a company with dozens of products and business considerations, someone can effectively place a financial wager on whether one specific clinical experiment succeeds. This new system represents a distinct break from traditional models of speculation in the biopharmaceutical space.

There are legitimate arguments in favor of prediction markets. They may aggregate dispersed information from physicians, scientists, investors, patients and others following a field. Their prices can create a continuously updated public estimate of how likely a trial

is to succeed. In theory, that may be more informative than analyst reports, corporate guidance or conventional expert opinion.

However, clinical trials are not football games. The people with the best information are sometimes helping determine the outcome being predicted. An investigator may know whether patients are completing visits, whether unexpected adverse events are occurring, whether recruitment has been unusually difficult, or simply whether the treatment appears to be performing differently than expected. In addition, while legally bound to be honest in their assessments, investigators can directly impact trial results

especially as it pertains to documentation of safety events, treatment decisions (when trials allow for physician discretion), and in some trials image interpretation.³ Trial leadership, data-monitoring committees, sponsor

employees, and consultants may know considerably more. A physician directly betting on the outcome of a trial he or she is conducting would therefore present an obvious ethical problem, even before debating whether a particular transaction technically violates securities law, platform rules or another regulation.⁴

The more interesting problem, however, may involve physicians who never place a bet at all. Imagine an investigator posting that she is “very excited about what we’re seeing with the X trial.” A prominent physician likes a sponsor’s post about an upcoming data presentation. Someone says on a podcast that a

(Continued on page 38)



BIO

Dr. Sridhar is an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute, Miami.

DISCLOSURES

Dr. Sridhar is a consultant to Alcon, DORC, Genentech/Roche and Regeneron Pharmaceuticals.

New approaches to diagnosing and managing PVR

Combining advanced microstructural imaging, novel surgical techniques, and emerging pharmacotherapy to improve outcomes in complex retinal detachments.

By Ajay Kuriyan, MD, and Omar Masoud, MD



Ajay Kuriyan, MD



Omar Masoud, MBBS

Take-home points

- » Standardized PVR grading and novel OCT staging systems provide critical clinical frameworks for predicting disease progression and surgical complexity.
- » Imaging biomarkers, such as evaluating retinal hyperreflectivity, offer non-invasive methods to assess pre-clinical PVR and prognosticate surgical outcomes.
- » Advanced traction-relieving surgical techniques, including ILM peeling and PFO-guided retinectomy, may improve anatomic outcomes in selected high-risk eyes.
- » Adjunctive pharmacotherapies, particularly intravitreal methotrexate, represent promising strategies for suppressing the cellular proliferation that drives PVR.

Proliferative vitreoretinopathy remains the most common and formidable cause of surgical failure in the treatment of rhegmatogenous retinal detachment.^{1,2} Characterized by the growth and contraction of fibrocellular membranes on both the retinal surfaces and within the vitreous cavity, PVR represents an exaggerated, protracted wound-healing response. Retinal pigment epithelial cells, glial cells, and inflammatory macrophages undergo epithelial-mesenchymal transition mediated by various cytokines and growth factors.^{3,4} This multifactorial fibroproliferative process mechanically distorts the retina, often inducing new retinal breaks or reopening existing ones.⁵ Despite major advances in vitreoretinal surgical techniques and instrumentation, preventing and managing severe PVR continues to challenge retina specialists worldwide. In this article, we outline novel and emerging approaches to diagnosing and managing PVR, highlighting advancements in clinical imaging, surgical techniques, and targeted pharmacotherapy.

1) Diagnosing PVR clinical criteria and pvr scoring

The foundation of PVR management begins with accurate clinical diagnosis and standardized grading. The first widely recognized classification system was published by The Retina Society Terminology Committee in 1983.⁶ This system categorized PVR based on clinical signs and geographic distribution into four progressive grades:

- **Grade A:** Vitreous haze and vitreous pigment clumps. This is the earliest clinical manifestation of the disease process.
- **Grade B:** Surface retinal wrinkling, rolled edges of retinal breaks, retinal stiffness and vessel tortuosity.
- **Grade C:** Full-thickness, fixed retinal folds. This was historically subdivided by the number of quadrants involved (C-1 to C-3).
- **Grade D:** Fixed retinal folds in all four quadrants forming a funnel detachment (D-1 wide, D-2 narrow, D-3 closed).

While the 1983 Retina Society classification laid the necessary groundwork, it was later updated to better account for anterior

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PVR and the exact types of contraction.⁷ Using a standard PVR scoring system is helpful in practice. Not only does it dictate the surgical approach, such as anticipating the need for an encircling scleral buckle, extensive membrane peeling or retinectomy, but it also standardizes patient cohorts for clinical trials and retrospective studies.

Imaging the PVR interface

While PVR has historically been a clinical diagnosis, advanced optical coherence tomography imaging has revolutionized our ability to identify its earliest microstructural precursors. The onset of PVR is marked by the intraretinal migration of macrophages, glial cells, and transdifferentiated RPE cells, which disrupt the retinal microarchitecture, and can appear as outer retinal hyperreflective dots on OCT before overt clinical signs appear.⁸

OCT findings and retinal reattachment physiology

Recent investigations by Muni and colleagues have utilized high-resolution OCT to characterize the *in vivo* physiology of retinal detachment and reattachment. Muni et al. developed a morphologic grading system that classifies RRD based on progressive OCT imaging features, ranging from neurosensory separation to the complete loss of photoreceptor inner and outer segments.⁹

Following procedures such as pneumatic retinopexy, normal retinal reattachment occurs in microstructural stages. Delayed progression through these reattachment stages is associated with postoperative anatomic abnormalities, including the formation of outer retinal folds, persistent subfoveal fluid blebs, and early epiretinal membrane formation.¹⁰ Identifying these early structural anomalies provides a window into the retina's mechanical stiffness and early cellular proliferation, alerting the surgeon to an increased risk of clinically significant PVR before macroscopic fixed folds appear.

Reflectivity in PVR

The optical properties of the detached retina and overlying membranes serve as profound biomarkers for PVR. Histopathological changes, such as the intraretinal migration of RPE cells and disorganized retinal layers, increase the backscatter of light on OCT.¹¹

In a recent study by our group, adjusted retinal pixel intensity (ARPI) was evaluated to quantify this hyperreflectivity and correlate it with the presence of PVR and postoperative outcomes.¹² ARPI calculates the difference between the mean pixel intensity of the detached neurosensory retina and the region of the vitreous directly overlying it. It was found that an increased ARPI was independently associated with the presence of Grade C PVR and lower rates of single-surgery anatomic success (SSAS). Notably, this trend was observed even in patients who didn't have clinically apparent PVR at the time of initial presentation, suggesting that quantifying retinal hyperintensity may serve as a valuable, non-invasive imaging biomarker to aid in preoperative risk stratification.¹³ By identifying high-risk eyes prior to surgery, retina specialists can potentially proactively employ surgical techniques such as internal limiting membrane peeling, or prophylactic pharmacotherapy, to optimize outcomes and prevent surgical failure.

2) Managing PVR surgical techniques

The surgical management of PVR requires meticulous relief of all mechanical traction. Once core and peripheral vitrectomies are complete, surgeons employ advanced techniques to ensure long-term anatomic success.

• Internal limit-



The contractile membranes of PVR result in generalized retinal shrinkage, fixed retinal folds, and characteristic "star folds," which are most evident from 4:00 to 11:00 in this photograph of a retinal detachment involving the macula.

Jesse Vitale, MD/Brice Crisier, CHAeyoung.org

These findings position TNF inhibitors as highly promising, targeted prophylactic agents for patients at high risk of PVR, particularly those with a history of smoking or chronic inflammation.

ing membrane peeling. The ILM acts as a primary scaffold for cellular proliferation in PVR. A robust body of literature supports the utility of ILM peeling in both primary high-risk RRDs and complex PVR cases.¹⁴ Peeling the ILM effectively removes the substrate upon which myofibroblasts and RPE cells migrate and contract.

In cases of uncomplicated retinal detachments, Shah and colleagues reported ILM peeling decreases rates of postoperative ERM formation.¹⁵ A small retrospective study of patients with Group B PVR found a higher single surgery success rate and less ERM formation in patients who underwent ILM peeling compared to patients who did not.¹⁶ Furthermore, a study by Wakabayashi and colleagues also demonstrates that primary ILM peeling during RRD with Grade C PVR repair reduces the incidence of retinal re-detachment and postoperative PVR.¹⁷ These studies support that ILM peeling in RD surgery with or without PVR may improve anatomical outcomes.

• **PFO-guided retinectomy.** In cases of advanced, severe Grade C PVR with intrinsic retinal shortening, retinectomy is often necessary.¹⁸ Historically, patients requiring retinectomy for Grade C PVR have faced guarded outcomes, with SSAS rates hovering between 61 and 67 percent at six months.¹⁹ Surgical failure in these complex cases is frequently caused by new fibrosis, missed fibrosis during the initial operation or intrinsic fibrosis and immature pre-retinal membranes that are difficult to visualize.

To combat these challenges, our team recently evaluated outcomes utilizing a novel Perfluoro-n-Octane (PFO)-guided retinectomy technique.²⁰ This technique leverages the identification of a deformation of the PFO bubble to visually identify the ideal posterior edge of the retinectomy, ensuring that all immature membranes and intrinsic fibrosis are adequately removed. Our data demonstrated that patients undergoing PFO-guided retinectomy achieved nearly an 89 percent SSAS rate at six months, representing a significant improvement over institutional his-

torical controls and the pooled historical controls used in recent major trials. This technique offers a potential effective strategy to improve surgical outcomes in eyes with Grade C PVR.

Medications: From past failures to promising horizons

While surgery expertly addresses the mechanical forces of PVR, resolving the underlying cellular proliferation requires targeted pharmacotherapy.

• **Past therapeutics.** Historically, numerous antimetabolites and anti-inflammatory agents have been investigated with underwhelming results. 5-fluorouracil (5-FU) and low-molecular-weight heparin (LMWH) were in the landmark PRIVENT trial.²¹ However, the findings were unable to be replicated in a subsequent study.²² Similarly, while intraocular corticosteroids effectively reduce postoperative inflammation, large-scale randomized trials have consistently failed to show a definitive reduction in overall PVR rates.²³

• **Tumor necrosis factor inhibitors.** Recent translational research has focused on the precise signaling cascades driving EMT in PVR. Cigarette smoke is an established, modifiable risk factor for PVR.²⁴ Laboratory research has elucidated that cigarette smoke extract significantly upregulates pro-inflammatory cytokines, specifically tumor necrosis factor-alpha (TNF- α), driving the EMT of RPE cells via the NF- κ B/Snail signaling axis. In murine models of PVR, inhibiting TNF- α or the downstream NF- κ B pathway blocks this transition and significantly reduces PVR severity.²⁵ These findings position TNF inhibitors as highly promising, targeted prophylactic agents for patients at high risk of PVR, particularly those with a history of smoking or chronic inflammation.

A small study of 60 patients examined the use of an intravitreal anti-TNF- α agent, infliximab, to inhibit PVR formation in patients with RRDs with Grade C PVR. There was a non-significant improved single surgery success rate in the infliximab

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group (26/30) compared to the control group (23/30). The treatment group had slightly better visual outcomes (Snellen equivalent $\approx$ 20/180) compared to the control group (Snellen equivalent $\approx$ 20/280; $p=0.044$).²⁶

• **Methotrexate.** While targeting specific signaling pathways like TNF offers a promising prophylactic strategy, combating the broader fibrocellular proliferation characteristic of established EMT requires potent antimetabolite therapy. In this regard, perhaps the most exciting development in the medical management of PVR is the use of intravitreal methotrexate. As an antimetabolite, methotrexate effectively inhibits the rapid proliferation of RPE and glial cells.

The Phase III GUARD trial provided encouraging evidence for adjunctive intravitreal methotrexate using ADX-2191. While eyes receiving ADX-2191 had a 24-percent rate of recurrent RD requiring reoperation compared to 39 percent in historical controls, the randomized comparison with routine surgical care didn't demonstrate a statistically significant difference (18.8 vs. 20.6 percent).²⁷ Therefore, these findings should be interpreted as promising rather than definitive, especially given the trial's substantial treatment burden of 13 injections over 16 weeks.

Corroborating this, early data from the FIXER trial, presented at ASRS, also support investigation of intraoperative methotrexate infusion followed by postoperative injections for PVR prevention.²⁸ Together, these data suggest that methotrexate may play an important adjunctive role for complex RDs and RDs with PVR.

Conclusion

The emerging approach to PVR is shifting from treating established mechanical contraction toward earlier identification of biologic risk and more targeted intervention. Quantitative imaging, refined surgical techniques, and adjunctive pharmacotherapy may ultimately allow treatments that improve visual and surgical outcomes in patients with PVR. Continued collaboration and rigorous clinical trials will be vital as we

refine these techniques and integrate them into standard clinical practice to ultimately improve patient outcomes. 

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How to avoid pitfalls in surgery for diabetic retinopathy

A discussion of the most common issues that can arise during surgical intervention and how to optimize surgical outcomes.

By Luis Acabá-Berrocal, MD and María H. Berrocal, MD

Take-home points

- » Diabetic retinopathy surgery is highly variable and technically difficult, with vitreous hemorrhage, tractional retinal detachment, and combined tractional–rhegmatogenous detachment being the main indications for surgery.
- » The biggest intraoperative risks are poor visualization, bleeding, and iatrogenic retinal breaks, so careful control of bleeding, maintenance of dilation, and use of high-speed small-gauge vitrectomy tools are key preventive strategies.
- » Postoperative vitreous hemorrhage is the most common complication, and minimizing it requires meticulous hemostasis, secure closure of sclerotomies, thorough retinal inspection, and adequate treatment of ischemic/neovascular tissue.

Surgical management of complications related to diabetic retinopathy remains challenging due to the heterogeneity of the disease. No two cases present in exactly the same way. The most common pathologies requiring surgical intervention include vitreous hemorrhage, tractional retinal detachment and combined tractional–rhegmatogenous retinal detachment.

In many diabetic eyes, the posterior hyaloid is partially attached and thickened, creating a scaffold for neovascularization. These neovascular complexes often form strong adhesions to the retina, making their removal technically demanding.

Complications during diabetic vitreoretinal surgery can be broadly classified into intraoperative and postoperative complications.

Intraoperative complications occur in approximately 13 to 30 percent of cases and include:

- bleeding during fibrovascular tissue dissection;
- iatrogenic retinal breaks caused by strong fibrovascular adhesions to a thinned

retina;

- poor intraoperative visualization due to prolonged surgery and elevated intraocular pressure in phakic eyes; and
- lens trauma and cataract formation.¹⁻⁵

Postoperative complications include:

- early or late postoperative vitreous hemorrhage (20 to 32 percent), the most common complication;
- cataract progression (18 to 21 percent) within one year;
- elevated intraocular pressure (~10 percent);
- neovascular glaucoma (5 to 9 percent); and
- rhegmatogenous retinal detachment.

Intraoperative pitfalls and their prevention

There are several issues to watch out for during surgery:

• **Poor intraoperative visualization.**

Poor visualization is common in diabetic eyes and may result from:

- inadequate pupillary dilation;
- corneal epithelial instability;
- intraoperative bleeding;



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- posterior synechiae; and
- lens opacities.

Maintaining adequate dilation throughout surgery is essential. Intracameral epinephrine and glucose-containing irrigation solutions may assist in maintaining dilation in phakic eyes.

Corneal clarity can be improved by topical glycerine, which helps reduce corneal edema. Mechanical corneal scraping should be avoided when possible, as diabetics are prone to persistent epithelial defects.

Iris hooks may be useful when dilation is inadequate. However, controlling intraoperative bleeding remains the most critical factor for maintaining good visibility.

Clear visualization of the peripheral retina during membrane dissection is essential because inadvertent traction in the periphery may occur during manipulation. Digital 3D visualization systems can improve magnification while maintaining a wide field of view, unlike traditional macular lenses used with standard microscope viewing.

• **Lens trauma in phakic eyes.** In phakic patients, inadvertent trauma to the lens can significantly impair visualization and may lead to rapid progression to a white cataract in the early postoperative period.

This complication can be minimized by avoiding crossing instruments across the vi-

sual axis toward the contralateral periphery and maintaining awareness of the posterior capsule location throughout surgery.

• **Intraoperative bleeding.** Intraoperative bleeding is the most frequent complication during diabetic vitrectomy. It typically occurs during segmentation or peeling of fibrovascular membranes and detachment of the posterior hyaloid. Bleeding significantly compromises visu-

alization and must be controlled promptly.

Key strategies to minimize bleeding include:

- ensuring adequate systemic blood pressure control during surgery;
- temporarily raising intraocular pressure during vessel segmentation;
- cauterizing vessels using endodiathermy or laser when necessary; and
- avoiding sudden IOP fluctuations, particularly hypotony.

Large blood clots forming over detached retina are difficult to remove and may lead to iatrogenic retinal breaks or hinder further membrane dissection.

• **Iatrogenic retinal breaks.** Avoiding iatrogenic retinal breaks during hyaloid removal and fibrovascular membrane dissection is critical, as such breaks are associated with a 2.5 to 3.9-fold increased risk of poor visual outcomes.⁸

If a break occurs, the surgeon must relieve surrounding traction, apply adequate laser treatment and consider long-term tamponade agents.

Although not always preventable, several strategies can reduce the risk:

• **Maintain optimal visualization at all times.** Tissue removal should never be attempted when visualization is poor.

• **Preoperative panretinal photocoagulation.** Peripheral PRP strengthens retinal adhesions and reduces traction-related breaks during surgery.

• **Early removal of peripheral vitreous.** Clearing vitreous adhesions at the beginning of the case reduces traction generated during intraocular maneuvers.

• **Identify a safe dissection plane.** Whenever possible, locate the plane between retina and fibrovascular tissue before initiating dissection.

• **Initiate dissection near the optic nerve.** If a plane isn't easily identifiable, detaching the hyaloid around the optic disc and progressing toward the periphery may be helpful.

Use small-gauge, high-cut-rate vitrectomy systems. Smaller gauges and higher cutting

Getty



Vitreous hemorrhage is one of the most common pathologies requiring surgical intervention in DR patients.

speeds minimize retinal traction during tissue removal. The 27-gauge vitrector can also be used to aspirate fibrovascular tissue gently, lifting membranes and revealing adhesion points. Compared with forceps, this technique reduces traction and lowers the risk of retinal breaks. When adhesions are strong, the limited aspiration force of the 27-gauge cutter often allows tissue to fall back rather than transmitting traction to the retina.⁹

- **Bimanual dissection in complex cases.** In complicated cases, particularly combined tractional and rhegmatogenous detachments, a chandelier illumination system allows for safe bimanual membrane dissection.

- **Preoperative anti-VEGF therapy.** In eyes with neovascular glaucoma or highly vascular membranes, preoperative anti-VEGF injections can significantly reduce intraoperative bleeding.

- **Viscodissection in highly adherent membranes.** When fibrovascular tissue is extremely adherent—particularly over rhegmatogenously detached retina—viscodissection may facilitate safer membrane separation.

- **Meticulous peripheral retinal inspection.** Before fluid–air exchange, the peripheral retina should be carefully examined using scleral depression to identify peripheral retinal breaks, vitreous base traction and traction originating from sclerotomy sites

Failure to identify these findings may lead to postoperative retinal detachment.

Postoperative problems and prevention

Here are the issues to be aware of in the postop period and how you can sidestep them:

- **Postoperative vitreous hemorrhage.** The most common postoperative complication is recurrent vitreous hemorrhage. Early postoperative hemorrhage is frequently related to perioperative hypotony.^{6,7} Preventive strategies include using smaller-gauge sclerotomies, suturing leaking sclerotomies at the end of surgery and using minimally

expansile gas concentrations when gas tamponade is required. Early hemorrhage may also result from residual intraocular clots and/or inadequately cauterized neovascularization. Sequentially lowering the IOP at the end of surgery can reveal active bleeding sites, allowing for targeted cauterization.

Another helpful technique is intraoperative fluorescein angiography, which enables identification of areas of ischemia or leakage that can be treated immediately. This approach has been shown to reduce postoperative bleeding.

Late postoperative hemorrhage may occur due to recurrent neovascularization from inadequate laser treatment, poor systemic blood pressure control and/or persistent intraocular traction.

- **Postoperative retinal detachment.**

Postoperative retinal detachment can be minimized by:

- thorough retinal inspection at the end of surgery;
- complete removal of traction surrounding retinal breaks;
- adequate laser photocoagulation around breaks; and
- marking breaks intraoperatively with diathermy to ensure they are clearly visible and adequately treated.

Conclusion

Avoiding surgical pitfalls during vitreoretinal surgery for diabetic retinopathy is critical for achieving optimal visual outcomes. Advances in vitrectomy technology, including high-speed cutters and small-gauge instrumentation, have significantly reduced traction on the retina. In addition, modern digital visualization systems enhance tissue contrast and improve identification of surgical planes.

Despite these technological advances, meticulous surgical planning, careful intraoperative technique and thorough postoperative management remain essential for successful outcomes in these complex cases.

(For a version with the full list of references, visit retina-specialist.com). 

The geographic atrophy therapeutic pipeline

Current and emerging clinical trials in geographic atrophy.

By Sunir Garg, MD, and Sonia Mehta, MD



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Take-home points

- » The GA treatment field has moved beyond complement inhibition alone, with multiple strategies now in development to slow progression, reduce treatment burden, and eventually restore retinal function.
- » Current approved complement inhibitors modestly slow lesion growth but don't restore vision, so future progress will likely depend on combination therapies, earlier intervention, and better patient selection.
- » The pipeline is broad and diverse—spanning visual cycle modulators, neuroprotective and mitochondrial therapies, lasers, implants, gene therapy, and stem cells—but most approaches remain investigational.

The treatment landscape for geographic atrophy secondary to age-related macular degeneration has undergone a dramatic transformation with the U.S. Food and Drug Administration approval of complement-inhibiting therapies. Despite these advances, significant unmet needs remain, as current treatments modestly slow lesion growth but, unfortunately, they can't restore vision. A broad range of therapeutic strategies are under active investigation, including complement pathway modulation, visual cycle inhibition, antioxidative therapies, reduction of toxic cellular byproducts, neuroprotection, laser-based interventions, photobiomodulation, surgical implants, gene therapy, stem cell therapies and mitochondrial enhancement. In this article, we'll discuss some of the new treatment programs currently in development.

Complement inhibition: The current standard and future directions

Dysregulation of the complement cascade remains one of the most extensively

studied mechanisms in GA pathogenesis. The two currently approved therapies target different components of the complement system: pegcetacoplan targets C3 and C3b and avacincaptad pegol targets C5.

• **Pegcetacoplan.** Pegcetacoplan is a pegylated peptide that binds complement C3/C3b and prevents downstream complement activation. In the Phase III OAKS trial, at 12 months, monthly and every-other-month intravitreal administration reduced overall GA lesion growth (foveal and non-subfoveal lesions combined) by 21 percent and 16 percent, respectively. Although the companion DERBY trial failed to meet its primary endpoint at 12 months, longer-term follow-up demonstrated benefit in both studies. At 24 months, monthly treatment reduced lesion growth by 22 percent in OAKS and 19 percent in DERBY, while every-other-month dosing reduced growth by 18 percent and 16 percent, respectively. This drug has also been approved by the FDA.

The ongoing GALE extension study has shown increasing treatment benefit over

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time, with up to a 42-percent reduction in lesion growth versus projected sham in the monthly treatment arm compared to projected sham at 36 month.¹

The GARLAND study (Apellis) is a Phase IV real-world study evaluating pegcetacoplan's long-term efficacy and safety. This is a post-marketing observational study that's expected to be completed in June 2027.

• **Avacincaptad pegol.** The Phase II/III GATHER1 study demonstrated that monthly intravitreal avacincaptad pegol reduced non-subfoveal GA lesion growth by 27 percent (35 percent when square-root transformation wasn't used) at 12 months compared with sham treatment.² These findings were subsequently supported by the Phase III GATHER2 trial, which reported a 14-percent reduction (18 percent if not calculated using square-root transformation) in non-subfoveal GA area growth at 12 months with monthly dosing.³ Two-year data was recently published and supported efficacy for both monthly (14-percent difference versus sham) and every-other-month (19-percent difference versus sham) dosing.⁴ These studies established C5 inhibition as an effective strategy for slowing GA progression and led to US FDA approval.

Ongoing complement-based trials

Several other complement inhibitors are in clinical development. We highlight a few of them here. There are several others in the pipeline, so please see clinicaltrials.gov for a more comprehensive evaluation.

• **Phase III programs.** The Archer II (Annexon) is a study of an intravitreal complement inhibitor called vonaprunten that's being evaluated for patients with central GA. Unlike the current treatments, it targets C1q, an essential part of the classic pathway but leaves the alternative and lectin pathways alone hopefully allowing normal immune function to occur more fully.

The Phase II ARCHER study failed to reduce GA lesion growth at 12 months

but demonstrated significantly less visual function loss. Only 6 percent of treated eyes lost ≥ 15 letters compared with 21 percent of sham eyes. The ongoing Phase III ARCHER II trial is evaluating ≥ 15 -letter vision loss at 18 months as its primary endpoint.

The SIENNA trial (Regeneron) is a Phase III study evaluating systemic complement inhibition for patients with GA. The study uses cemdisiran, a small interfering RNA (siRNA) that suppresses complement component C5, with or without pozelimab, a monoclonal antibody against C5. By inhibiting C5, the treatment aims to prevent formation of the membrane attack complex and reduce complement-mediated retinal damage.

The primary endpoint is GA lesion growth measured by fundus autofluorescence at one year. Unlike currently approved intravitreal complement inhibitors, SIENNA is investigating a subcutaneous systemic therapy, which may reduce treatment burden while providing sustained complement inhibition.

• **Phase II programs.** The GALLOP trial (Apellis Pharmaceuticals) is a Phase II study evaluating a combination complement inhibition strategy for patients with GA. Participants receive APL-3007, a subcutaneous siRNA that suppresses complement component C3 production, together with intravitreal pegcetacoplan, an approved C3/C3b inhibitor. The goal is to determine whether dual systemic and local inhibition provides greater protection against retinal degeneration than intravitreal therapy alone.

The primary endpoint is the change in retinal pigment epithelium lesion area measured by artificial intelligence-based OCT analysis at one year. This study is among the first to evaluate whether combining systemic and intravitreal complement inhibition can improve treatment outcomes in GA.

The VERDANT trial (Boehringer Ingelheim) is a Phase II study evaluating

Dysregulation of the complement cascade remains one of the most extensively studied mechanisms in GA pathogenesis.

BI771716, an intravitreal monoclonal antibody fragment targeting the complement pathway, in patients with GA. The study directly compares BI771716 with pegcetacoplan, making it one of the few head-to-head trials between investigational and approved complement therapies.

The primary endpoint is the slope of change in square root-transformed GA lesion area on fundus autofluorescence through 56 weeks. The trial is designed to determine whether BI771716 can slow GA progression as effectively as, or better than, the current standard of care while further characterizing its safety profile.

The JADE study (Boehringer Ingelheim) is a Phase II study evaluating BI1484-0005, a daily oral PAF receptor antagonist. BI1484-0005 targets the PAF receptor which is involved in inflammation, angiogenesis and vascular permeability. The primary endpoint is slope of change from baseline in square-root transformed GA area, as measured by FAF at 50 weeks.

Another Phase II trial is evaluating iptacopan (LNP023), an oral complement factor B, for patients with early and intermediate AMD. This trial is evaluating the progression to GA at two years.

Visual cycle modulation

Visual cycle modulators aim to reduce accumulation of toxic vitamin A-derived byproducts implicated in retinal pigment epithelium dysfunction and photoreceptor

loss.

ALK-001 (gildeuretinol), a deuterated vitamin A derivative, is designed to reduce vitamin A dimerization and subsequent formation of toxic retinal byproducts. Although the therapy didn't demonstrate a statistically significant reduction in GA growth through 24 months, post hoc analyses suggested a 15.3-percent reduction in lesion growth between months six and 24. Further studies may clarify whether earlier intervention or patient selection could enhance treatment benefit. The Phase III study is fully enrolled, and results are expected in December 2026.

Belite Bio's Phase III PHOENIX study also targets the visual cycle. This oral therapy aims to reduce the accumulation of toxic vitamin A-derived byproducts implicated in retinal degeneration and may offer a noninvasive treatment alternative for patients with GA. The PHOENIX study is fully enrolled, and results are expected in August 2027.

Antioxidative therapies

Oxidative stress remains a central mechanism in AMD pathogenesis. Antioxidant supplementation has long been investigated as a strategy to slow disease progression.

The landmark AREDS trial demonstrated a 25-percent reduction in progression to advanced AMD with antioxidant and zinc supplementation. However, this benefit was primarily driven by reduced progression to neovascular AMD rather than prevention of GA enlargement. AREDS2 subsequently replaced β -carotene with lutein and zeaxanthin and suggested a potential slowing of central GA progression.⁵ In a post-hoc analysis of AREDS2, patients with non-central GA experienced slower rate of growth toward the center of the macula.⁶

Current investigations include EG-301 (EG-DPMP-01, Evergreen Therapeutics, NCT05170048), which is undergoing Phase II evaluation to slow GA area expansion at 26 weeks. This is an oral ther-

Table 1. Prior failed complement-based clinical trials

Drug	Phase and Name	Mechanism
Lampalizumab	Phase III CHROMA and SPECTRI	Factor D inhibitor
Eculizumab	Phase II complete	C5 inhibitor
Tesidolumab/LFG316	Phase II	C5 inhibitor
CLG561	Phase II	Properdin inhibitor
POT-4	Phase II	C3 inhibitor
GEM103	Phase Iia ReGAtta	Complement factor H replacement
NGM621	Phase II CATALINA	C3 inhibitor
IONIS-FB-LRx	Phase II GOLDEN	Complement factor B inhibitor

apy that targets choriocapillaris, retinal and RPE oxidative stress, though the exact mechanism remains proprietary.

Reduction of toxic cellular byproducts

Accumulation of toxic protein aggregates and retinal waste products may contribute to RPE degeneration and photoreceptor death. GAL-101 (MRZ-99030, Galimedix Therapeutics, NCT06659549) is being investigated via the eDREAM study. This is a topical ophthalmic drop that targets beta amyloid oligomers. Primary completion is expected in March 2027.

This class of therapy seeks to reduce cellular toxicity and preserve retinal structure before irreversible atrophy develops.

Neuroprotective therapies

Neuroprotection represents another promising strategy aimed at preserving photoreceptors and retinal neurons despite ongoing disease processes.

Risuteganib (Luminate, ALG-1001) is currently being evaluated in a Phase II clinical trial. By targeting integrin signaling pathways, risuteganib may improve cellular resilience and retinal function independent of complement modulation. Risuteganib is thought to function by binding to RPE cells to reduce mitochondrial reactive oxygen species, reducing RPE cell death due to oxidative stress.⁷

Laser-based therapies

Laser interventions are being explored as potential methods to modulate retinal metabolism and stimulate protective cellular responses. The Laser Intervention in Early Stages of Age-Related Macular Degeneration (LEAD) study was a 36-month trial conducted in Australia that evaluated sub-threshold nanolaser in 292 patients with intermediate AMD to assess the progression to GA. Subthreshold nanolaser produces a non-visible laser spot that's thought to function by modulating RPE-mediate turnover of, and reduce outflow resistance at, Bruch's membrane. This study failed to

meet its primary endpoint, though post-hoc analysis suggests patients without reticular pseudodrusen may experience slowed progression to GA.⁸ Another clinical trial is underway in Australia evaluating the R:GEN Laser System (LASER LIGHT-01) on progression to GA.⁹

Photobiomodulation

Photobiomodulation uses specific wavelengths of light to improve mitochondrial function and reduce oxidative stress.

The Valeda Light Delivery System has been evaluated in the LIGHTSITE I, II and III clinical trials. The LIGHTSITE III study enrolled 148 eyes with intermediate dry AMD or non-foveal GA which and randomized them to receive either photobiomodulation or sham therapy, three times per week over three to five weeks, every four months for two years (total of 52 treatment sessions). Study patients exhibited significantly lower incidence of progression compared to sham (6.8 versus 24 percent).¹⁰ The proposed mechanism for PBM is mitochondrial photoreceptor activation to produce a biologic response that stabilizes metabolic function, promotes cytoprotection and produces energy.¹⁰

Surgical and implantable technologies

Advanced visual prosthetic and implantable technologies seek to restore function in patients with advanced atrophic disease. The PRIMA (Photovoltaic Retina Implant Microarray System) bionic vision system uses a 2 x 2 mm photovoltaic subretinal chip with 378 pixels, camera-equipped smart glasses and a processor to bypass dead photoreceptors and stimulate intact retinal cells with infrared light.¹¹

Another implantable device, the SING-IMT implant, acts as an intraocular Galilean telescope, providing 2.7-fold magnification, and projecting images onto areas of healthy retina.¹² The OcuDyne OPTiC is a minimally invasive device that performs ophthalmic artery angioplasty to improve ocular blood flow in patients with GA.¹³

Trial	Sponsor	Phase	Status	Route of Administration	Patient Population	Mechanism of Action	Primary Endpoint	Estimated Completion	Trial NCT
ARCHER II (ANX007, vonaprumment)	Annexon	Phase III	Active, not recruiting	Intravitreal injection	GA	C1q inhibitor; blocks classical complement pathway	≥15-letter loss from baseline at 15 months	Primary completion: October, 2026 Study completion: July, 2027	NCT06510816
Danicopan (ALXN2040)	Alexion (Astra-Zeneca)	Phase II	Terminated, lack of efficacy	Oral	GA	Small molecule inhibitor of complement factor D, blocks the alternative pathway	Safety, efficacy, and dose escalation trial	Terminated	NCT05019521
GALLOP (APL-3007)	Apellis Pharmaceuticals	Phase II	Recruiting	Subcutaneous injection (APL-3007) + intravitreal injection (pegcetacoplan)	GA	siRNA targeting C3 (APL-3007) used with pegcetacoplan (anti-C3, C3b)	Change in the area of artificial intelligence-based OCT assessment of RPE lesion at 1 year	Primary completion: June, 2027 Study completion: November, 2027	NCT07215390
GARLAND (pegcetacoplan)	Apellis Pharmaceuticals	Phase IV	Active, not recruiting	Intravitreal injection	GA	Synthetic cyclic peptide, complement C3 and C3b inhibitor	Long-term safety and effectiveness	Primary completion: June, 2027 Study completion: June, 2027	NCT06161584
Iptacopan (LNP023)	Novartis	Phase II	Active, not recruiting	Oral	Early and intermediate AMD	Small molecule inhibitor of complement factor B, blocks the alternative pathway	Progression to GA at 2 years	Primary completion: October, 2026 Study completion: October, 2026	NCT05230537
JADE (BI1484-0005)	Boehringer Ingelheim	Phase II	Active, not recruiting	Oral	GA	Oral complement inhibitor with a phospholipid modulator	Slope of change from baseline in square root transformed GA area on fundus autofluorescence at 50 weeks	Primary completion: February, 2027 Study completion: February, 2027	NCT06769048
SIENNA (cemdisiran +/- pozelimab)	Regeneron Pharmaceuticals	Phase III	Recruiting	Subcutaneous injection	GA	Cemdisiran (ALN-CC5) (C5 small-interfering RNA (siRNA)) +/- Pozelimab (REGN3918) (anti-C5 mAb)	GA lesion growth on fundus autofluorescence at 1 year	Primary completion: November, 2029 Study completion: May, 2032	NCT06541704
VERDANT (BI771716)	Boehringer Ingelheim	Phase II	Active, not recruiting	Intravitreal injection	GA	Monoclonal antibody fragment targeting complement versus pegcetacoplan	Slope of change from baseline in square root transformed GA area on fundus autofluorescence at 56 weeks	Primary completion: October, 2026 Study completion: October, 2026	NCT06722157
ALK-001 (Gildeuretinol)	Alkeus Pharmaceuticals	Phase III/Extension	Active, not recruiting	Oral	GA	Deuterated vitamin A	GA progression	Primary completion: December, 2026 Study completion: December, 2026	NCT04239625
EG-301	EyeGate Pharmaceuticals	Phase II	Not yet recruiting	Intravitreal	Non-focal GA	Oral small-molecule inhibitor of acid sphingomyelinase to reduce retinal oxidative stress	Safety, GA lesion size change by fundus autofluorescence, retinal sensitivity by microperimetry, mean change in BCVA, low-luminance VA, binocular reading speed, binocular critical print size, NEI-VFQ score at 26 weeks	Primary completion: June, 2028 Study completion: June, 2028	NCT05170048
PHOENIX (LBS-008, tinlarebant)	Belite Bio	Phase III	Active, not recruiting	Oral	GA	Visual cycle modulator reducing vitamin A byproducts via an oral retinol binding protein 4 (RBP4) antagonist	GA lesion rate of change (growth rate slope) on fundus autofluorescence at 2 years	Primary completion: June, 2027 Study completion: August, 2027	NCT05949593
Risuteganib (Luminate)	Allegro Ophthalmics	Phase II	Completed	Intravitreal injection	Intermediate AMD	Synthetic oligopeptide that inhibits integrin homodimers, blocking downstream pathways responsible for angiogenesis, inflammation, and vascular permeability	Change in BCVA at 28 weeks	Completed: April, 2019	NCT03626636

Trial	Sponsor	Phase	Status	Route of Administration	Patient Population	Mechanism of Action	Primary Endpoint	Estimated Completion	Trial NCT
LIGHTSITE III (Valeda)	LumiThera	N/A	Completed	Light therapy	Intermediate AMD and non-foveal GA	Photobiomodulation improving mitochondrial function	BCVA at 21 months	Primary completion: June, 2022 Study completion: June, 2022	NCT04065490
ARMADA (OCU410)	Ocugen	Phase III	Active, not recruiting	Subretinal gene therapy	GA	Subretinal AAV vector to deliver human Retinoid-related Orphan Receptor Alpha (RORA)	Safety, change in anatomy of ocular structures via slit lamp/indirect ophthalmoscopy, change in BCVA, LLVA, IOP at 12 months	Primary completion: February, 2026 Study completion: May, 2026	NCT06018558
Complement Opti-Gain (CTx001)	Complement Therapeutics	Phase I/II	Recruiting	Subretinal gene therapy	GA	AAV mini-CR1 gene therapy	Safety	Primary completion: May, 2028 Study completion: June, 2032	NCT07392255
GT005 (Focus)	Gyroscope Therapeutics/ Novartis	Phase I/II	Terminated, lack of efficacy	Subretinal gene therapy	GA	AAV-complement factor I gene therapy	Safety	Terminated: June, 2025	NCT03846193
GT005 (EXPLORE)	Gyroscope Therapeutics/ Novartis	Phase II	Terminated, lack of efficacy	Subretinal gene therapy	GA	AAV-complement factor I gene therapy	GA progression from baseline on FAF at 48 weeks	Terminated: April, 2024	NCT04437368
GT005 (HORIZON)	Gyroscope Therapeutics/ Novartis	Long-term Follow-up	Terminated, lack of efficacy	Subretinal gene therapy	GA	AAV-complement factor I gene therapy	Long-term safety	Terminated: June, 2024	NCT04566445
JOURNEY (VOY-101)	Perceive Biotherapeutics	Phase II	Recruiting	Intravitreal gene therapy	GA	Gene therapy with adeno-associated viral (AAV) vector to produce complement factor H protein	Safety	Primary completion: June, 2027 Study completion: March, 2028	NCT06087458
SAR446597	Sanofi	Phase I/II	Recruiting	Intravitreal gene therapy	GA	Gene therapy with AAV vector to produce antibody fragments that inhibit C1s (classical pathway) and Factor Bb (alternative pathway)	Safety	Primary completion: October, 2027 Study completion: July, 2032	NCT07215234
ASP7317	Astellas	Phase Ib	Active	Subretinal RPE transplant	GA	Human embryonic stem cell-derived RPE transplantation	Safety	Primary completion: June, 2026 Study completion: June, 2026	NCT03178149
CPCB-RPE1	Regenerative Patch Technologies	Phase I/IIa	Completed, unknown status	Subretinal RPE-scaffold transplant	GA	Human embryonic stem cell-derived RPE cells cultured on a parylene membrane	Safety	Primary completion: July, 2019 Study completion: June, 2023	NCT02590692
JUMPER/GAlette (GR44251)	Genentech / Lineage Cell Therapeutics	Phase IIa	Recruiting	Subretinal RPE transplant	GA	Human embryonic stem cell-derived RPE transplantation	Safety and integration	Primary completion: March, 2031 Study completion: March, 2031	NCT05626114
MA09-hRPE	Astellas	Phase I/II	Completed	Subretinal RPE transplant	GA	Human embryonic stem cell-derived RPE transplantation	Safety	Primary completion: August, 2019 Study completion: August, 2019	NCT01344993
SCOTS2	SCOTS Study Group	Phase 1	Recruiting	Intravenous / Retrobulbar / Intravitreal autologous stem cells	Optic nerve damage and retinal degeneration including GA	Autologous bone marrow-derived stem cells	Visual acuity at 12 months	Primary completion: July, 2031 Study completion: July, 2031	NCT03011541
RENEW (Elamipretide)	Stealth BioTherapeutics	Phase III	Active, not recruiting	Subcutaneous injection	GA	Mitochondria-targeting peptide stabilizing cardiolipin	GA growth and low-luminance visual function	Primary completion: August, 2027 Study completion: September, 2027	NCT06373731

Gene therapy offers the possibility of sustained therapeutic protein production following a single intervention.

Gene therapy

Gene therapy offers the possibility of sustained therapeutic protein production following a single intervention. Generally, these therapeutics work by transferring genetic material, either DNA or RNA, into the cells of the patient. There are four approaches to gene therapy, including gene replacement of a mutated gene, gene editing to correct a mutated gene, gene silencing via mRNA degradation with cytosolic proteins and modifying gene expression.¹⁴

Complement Therapeutics is investigating a subretinal gene therapy. Gene therapy has the potential advantage of providing a one-time treatment that continuously produces a complement regulatory protein within retinal cells rather than requiring repeated intravitreal injections. This gene encodes mini-CR1 (Complement Receptor 1) using an adeno-associated virus vector. Mini-CR1 is designed to regulate multiple complement pathways, including both the classical and alternative pathways.

Sanofi is investigating a one-time intravitreal AAV gene therapy. Like Complement Therapeutics' CTx001, it aims to provide long-lasting complement inhibition after a single injection but delivers genes encoding two complement regulatory proteins: CD46 (membrane cofactor protein) that regulates activation at the C3 level; and CD59 that inhibits formation of the membrane attack complex (MAC, C5b-9).

• **Currently enrolling studies.** The JOURNEY study (VOY-101, PerceiveBio, NCT06087458) is investigating phase I/II, intravitreal gene therapy that uses an AAV vector to transfect a complement factor H gene product. DFI18231 (SAR446597, Sanofi, NCT07215234) is a Phase I/II study evaluating an intravitreal gene therapy, using an AAV vector to promote the production of antibody fragments that inhibit C1s and Factor Bb, targeting both the classical and alternate pathway.

• **Ongoing studies.** The ArMaDa study (OCU410, Ocugen, NCT06018558) is an active Phase III program that's evaluating

subretinal delivery of human Retinoid-related Orphan Receptor Alpha (hRORA). This therapy targets cellular homeostasis via modulation of inflammation, oxidative stress, lipid metabolism and complement pathways.¹⁵

• **Pending studies.** Complement Opti-Gain (CTx001, Complement Therapeutics, NCT07392255) is a Phase I/II program that evaluates subretinal delivery of an AAV vector to produce mini-Complement Receptor 1 (mini-CR1). Mini-CR1 potentiates factor-I-mediated cleavage of C3b, iC3b and C4b, inhibiting both the classical and alternative pathways.

If successful, gene therapy could potentially overcome the treatment burden associated with repeated intravitreal injections.

Stem cell-based therapies

Cell replacement strategies aim to restore damaged retinal pigment epithelium and preserve photoreceptor survival.

• **Currently enrolling.** JUMPER (GR44251, Lineage Cell Therapeutics/Genentech, NCT05626114) is a Phase IIa program to evaluate embryonic stem cell RPE transplantation.

• **Ongoing studies.** Studies evaluating subretinal delivery of human embryonic stem cell-derived RPE cells include MA09-hRPE (Astellas, NCT01344993, Phase I/II) and ASP7317 (Astellas, NCT03178149, Phase Ib). There's early data that provides evidence of graft stability and efficacy for ASP7317.¹⁶ Other platforms are investigating RPE transplantation on a biodegradable polymer scaffold (CPCB-RPE1, Regenerative Patch Technologies, Phase I/IIa, NCT02590692) and autologous bone marrow-derived stem cell transplantation for optic nerve and retinal disease, including GA (SCOTS2, SCOTS Study Group, Phase I, NCT03011541).

These programs represent some of the most ambitious efforts in regenerative ophthalmology and may ultimately provide restorative treatment options for advanced disease.

Mitochondrial enhancement

Mitochondrial dysfunction has emerged as a potential contributor to retinal degeneration. Elamipretide, a mitochondria-targeting peptide, was evaluated in the ReCLAIM-2 study. The therapy is designed to improve mitochondrial structure and function, increase cellular energy production and reduce reactive oxygen species generation.¹⁷

Although ReCLAIM-2 failed to meet its primary endpoints of low-luminance visual improvement and reduction in GA growth, elamipretide demonstrated a significant reduction in ellipsoid zone attenuation compared with placebo at 48 weeks. These findings suggest that mitochondrial preservation may remain a viable therapeutic target despite mixed clinical outcomes.¹⁷ The Phase III RENEW trial is evaluating subcutaneous elamipretide for GA.

Looking ahead: Precision medicine

As the therapeutic landscape continues to evolve, future studies will likely incorporate increasingly sophisticated patient stratification strategies. Polygenic risk scores may identify individuals with high-risk complement variants and other susceptibility loci who are most likely to benefit from targeted interventions. Similarly, imaging and molecular biomarkers may help identify patients with active disease who are most likely to respond to therapy.

The future of GA treatment will likely extend beyond complement inhibition alone. Combination therapies targeting multiple pathogenic pathways, coupled with precision medicine approaches and earlier intervention, may ultimately provide greater preservation of vision and improved quality of life for patients with this devastating disease.

Several themes have emerged across the current clinical development landscape. First, we increasingly are pursuing therapies that reduce treatment burden through oral, subcutaneous or one-time gene therapy approaches. Second, there's a growing

recognition that structural endpoints alone may not fully capture clinically meaningful treatment effects, leading some studies to incorporate visual function and reading performance outcomes. Finally, regenerative medicine approaches are shifting the field beyond disease modification toward the possibility of tissue restoration. 

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A review of tyrosine kinase inhibitors in development

A look at the current results of these experimental agents, including those with alternate forms of delivery.

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Take-home points

- » Tyrosine kinase inhibitors are small molecules that act intracellularly to inhibit VEGF receptor signaling, resulting in broader VEGF suppression than extracellular anti-VEGF antibodies.
- » Paired with sustained-release platforms, intravitreal TKIs aim to extend dosing intervals to 6 to 12 months across nAMD, DME and NPDR.
- » Axitinib intravitreal hydrogel (Axpaxli) showed superiority to aflibercept in SOL-1 (Phase III) in patients with treatment-naïve nAMD that responded to aflibercept. Other Phase III trials involving Axpaxli (SOL-R) and the vorolanib insert Duravyu (LUGANO/LUCIA) are positioned for—or have already delivered—pivotal readouts in 2026.
- » TKIs with alternative forms of delivery—including suprachoroidal, periocular, topical and subcutaneous approaches—are under investigation.

Vascular endothelial growth factor suppression is the mainstay of treatment for neovascular age-related macular degeneration, diabetic macular edema and macular edema from retinal vein occlusion. For many of our patients, this has transformed blinding eye diseases into treatable conditions.

The most widely used treatment involves intravitreal injections every four to 16 weeks of antibodies or antibody fragments that block extracellular VEGF-A binding (as well as other growth factors such as VEGF-B, placental growth factor and angiopoietin-2, depending on the therapeutic agent that's used).

Because patients often require many injections, real world outcomes that we see in our practices tend to fall short of clinical trial results due to the burdens of frequent clinic visits.¹

Consequently, there remains an unmet need for treatments offering increased efficacy and durability.

Why TKIs?

VEGF receptors belong to a class of molecules called receptor tyrosine kinases. Tyrosine kinase inhibitors are small molecules that act intracellularly, blocking the signal transduction cascade that occurs after VEGF and other growth factors bind to their extracellular receptors. The downstream activity of TKIs allows for greater suppression of VEGF and other cytokines implicated in retinal vascular disease. The receptors central to these agents are the three VEGF receptors (VEGFR-1, -2 and -3), which transduce signaling for VEGF-A, -B, -C, -D, -E and placental growth factor. Several investigational TKIs additionally inhibit platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and c-Kit, which may influence pericyte recruitment and vascular maturation.²

Free TKI is rapidly cleared from the vitreous, so these agents are paired with sustained-release or alternative-delivery

BIOS

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platforms. Their small molecular weight (≤ 500 Da) and lipophilicity allow formulation in sustained-release vehicles, making them attractive candidates for chronic, relapsing retinal disease.³ The agents reviewed below are grouped by delivery route (intravitreal, suprachoroidal, periorbital, topical and subcutaneous), with indications spanning nAMD, DME and NPDR.⁴

Intravitreal sustained-release implants

Intravitreal delivery is currently the most popular route of administration, and includes the following implants:

- **Vorolanib intravitreal insert (EYP-1901/Duravyu, EyePoint Pharmaceuticals).** Duravyu is a bioerodible intravitreal insert combining vorolanib (a multikinase inhibitor of VEGFR-1, -2, -3, PDGFR β and c-Kit that is structurally related to sunitinib, but spares TIE2 at clinically relevant doses²) with the Durasert E platform, a newer bioerodible version of the Durasert sustained-release technology used in the fluocinolone acetonide insert Iluvien. Duravyu is injected in-office through a 22-gauge needle and is designed to deliver zero-order drug release for at least six months, without the need for refrigeration.⁵

In the Phase II DAVIO 2 trial, 161 previously treated patients with nAMD received three monthly aflibercept 2 mg loading doses and were then randomized 1:1:1 to a single intravitreal injection of vorolanib 2 mg, a single injection of vorolanib 3 mg or continued aflibercept 2 mg every eight weeks.⁶ Both vorolanib doses demonstrated noninferior best-corrected visual acuity and central subfield thickness compared with aflibercept, with an approximately 80-percent reduction in treatment burden. At 14 months, 43 percent of the 2-mg arm and 46 percent of the 3-mg arm remained supplement-free.⁶

Two Phase III trials, LUGANO and LUCIA are evaluating Duravyu 2.7 mg

on a six-month redosing schedule against on-label aflibercept in treatment-naïve and previously treated nAMD.⁷ In LUGANO, Duravyu didn't meet the primary vision endpoint for non-inferiority to aflibercept in the overall population, though it did successfully cut the required number of injections. Non-inferiority was only achieved in an ad hoc analysis that omitted a small patient subgroup.

The Phase II VERONA trial in DME met its primary endpoint, with 73 percent of patients in the Duravyu 2.7-mg arm supplement-free through week 24 versus 50 percent in the aflibercept arm, alongside BCVA gains of approximately +7 letters and CST reduction of -90 μ m at week four.⁸ Phase III trials in DME (COMO, CAPRI) are initiating enrollment. The Phase II PAVIA trial in moderate-to-severe nonproliferative diabetic retinopathy didn't meet its primary endpoint of ≥ 2 -step DRSS improvement at nine months. Disease stabilization was observed in 86 percent and 80 percent of the 3 mg and 2 mg arms versus 70 percent of sham. EyePoint has subsequently prioritized DME (COMO/CAPRI) for Duravyu's diabetic indication.⁹

- **Axitinib intravitreal hydrogel (OTX-TKI/Axpaxli, Ocular Therapeutix).** Axpaxli is a fully bioresorbable intravitreal hydrogel implant delivered through a 25-gauge needle, designed to elute axitinib over nine to 12 months via the Elutyx platform.¹⁰ Axitinib is an FDA-approved oral inhibitor used in renal cell carcinoma, with high potency against VEGFR-1, -2 and -3.²

In February 2026, Ocular Therapeutix reported positive topline results from SOL-1.¹¹ SOL-1 randomized 344 treatment-naïve patients that achieved 20/20 vision or gained at least 10 ETDRS letters with CST of 350 μ m or less after an 8-week loading period of two monthly aflibercept injections 1:1 to a single intravitreal injection of Axpaxli 0.45 mg or aflibercept 2 mg. Under the FDA Special

Protocol Assessment, 74.1 percent of Axpaxli-treated patients maintained visual acuity (defined as losing fewer than 15 ETDRS letters) at week 36, compared with 55.8 percent in the aflibercept arm, a risk difference of 17.5 percent ($p=0.0006$). The treatment effect persisted at week 52 (65.9 vs 44.2 percent; risk difference 21.1 percent, $p<0.0001$). This was the first Phase III superiority trial of a TKI in nAMD. Criticisms of the trial design include the selection for best responders and the strict criteria for rescue aflibercept.¹²

The complementary Phase III noninferiority study (SOL-R) is ongoing, and a separate Phase III program in NPDR has received FDA agreement under a Special Protocol Assessment following Phase III HELIOS data that demonstrated no progression to proliferative diabetic retinopathy or center-involving DME in the OTX-TKI arm versus 37.5 percent of sham controls at 48 weeks.¹³

• **Other intravitreal axitinib implants.** Additional intravitreal axitinib

implants in earlier development include AR-14034 (Alcon), a sustained-release implant in the Phase I/II NOVA-1 trial,¹⁴ and GLK-401 (Glaukos Corporation), an axitinib implant in Phase II trials for both nAMD and DME.

Alternative delivery routes

There are also potential therapies that don't use the intravitreal route:

• **Suprachoroidal axitinib injectable suspension (CLS-AX, Clearside Biomedical).** CLS-AX is a suprachoroidal injectable suspension of axitinib, the same VEGFR-1, -2, -3 inhibitor used in Axpaxli, delivered to the suprachoroidal space via Clearside's SCS Microinjector for nAMD. Suprachoroidal delivery via Clearside's microneedle compartmentalizes drug to the choroid and outer retina while limiting anterior segment exposure. In the Phase IIb ODYSSEY trial (n=60, randomized 2:1 to CLS-AX 1 mg or aflibercept 2 mg), CLS-AX demonstrated stable BCVA and CST noninferior

Table 1. Comparative Summary of Investigational TKIs

Agent (platform)	Sponsor	Delivery	Target	Indications	Key trial / phase
Vorolanib insert (Duravyu/EYP-1901)	EyePoint Pharmaceuticals	IVT bioerodible insert (Durasert E)	VEGFR-1/2/3, PDGFR β , c-Kit	nAMD, DME	LUCIA Phase III; LUGANO Ph III primary not met; VERONA Phase II met.
Axitinib hydrogel (Axpaxli/OTX-TKI)	Ocular Therapeutix	IVT bioresorbable hydrogel (ELUTYX)	VEGFR-1/2/3	nAMD, NPDR	SOL-1 Phase III superiority met. SOL-R Phase III. HELIOS Phase I met.
CLS-AX (axitinib)	Clearside Biomedical	Suprachoroidal injection	VEGFR-1/2/3	nAMD	Phase IIb met
Migaldendranib (D-45172)	Ashvattha Therapeutics	Subcutaneous nanomedicine	VEGFR (dendrimer conjugate)	nAMD, DME	Phase II
Tivozanib drops (KHK4951)	Kyowa Kirin	Topical eye drops	VEGFR-1/2/3	nAMD, DME	Phase II missed primary in nAMD
PAN-90806	Zhaoko Ophthalmology	Topical eye drops	VEGFR-2	nAMD	Phase II
AIV-007 (lenvatinib)	AIViva BioPharma	Periocular	Multi-kinase (VEGFR, FGFR, PDGFR)	nAMD, DME	Phase I
GLK-401 (axitinib)	Glaukos Corporation	IVT implant	VEGFR-1/2/3	nAMD, DME	Phase II

Abbreviations: IVT, intravitreal; nAMD, neovascular age-related macular degeneration; DME, diabetic macular edema; NPDR, non-proliferative diabetic retinopathy; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor.

to aflibercept every eight weeks, with an 84-percent reduction in supplemental anti-VEGF injections and approximately 67 percent of patients requiring no rescue therapy through six months.¹⁵ A Phase III program is planned following an end-of-Phase II meeting with the FDA. The exact execution of the Phase III program will be up to the Health Ocean Pharma company, which is in the process of acquiring Clearside's assets as part of Clearside's Chapter 11 bankruptcy filing.

- **Periocular lenvatinib gel depot (AIV-007, AiViva BioPharma).** AIV-007 (lenvatinib, AiViva BioPharma) is administered as a periocular flowable gel depot of a broad-spectrum TKI (targeting VEGFR-1, -2, -3, PDGFR, FGFR, RET and c-Kit) and is in Phase I trials for nAMD and DME.¹⁶ In a preliminary readout of the 18-patient Phase I trial, BCVA improved by up to 16 letters at 84 days, declining to up to four letters by 168 days, with stable or improved CST in the four patients completing 168 days.¹⁶

- **Topical TKIs.** Two topical TKIs are in active Phase II development. KHK4951 (tivozanib eye drops, Kyowa Kirin) is a nano-crystallized formulation of the FDA-approved oral TKI tivozanib (a selective inhibitor of VEGFR-1, -2 and -3), dosed topically for nAMD and DME.¹⁷ A Phase I dose-escalation study in Japan (116 patients across three cohorts, including 28 patients with nAMD) demonstrated CST reductions of 27 to 44 μ m across dose levels in the nAMD cohort, with BCVA stability.¹⁷ Reversible punctate keratitis was observed in 14 percent of nAMD patients and 47 percent of the healthy multi-dose cohort. The drop missed the primary endpoint in its Phase II trial.

PAN-90806 (Zhaoke Ophthalmology) is a selective inhibitor of VEGF-receptor signaling in Phase II testing as a once-daily topical drop. In a Phase I/II dose-ranging trial of 51 treatment-naïve patients with nAMD, more than half completed 12

weeks without requiring rescue intravitreal anti-VEGF injection.¹⁸ Corneal adverse events occurred in 9.8 percent of patients.

- **Subcutaneous migaldendranib (D-4517.2, Ashvattha Therapeutics).** Migaldendranib is a combined TKI and conjugate complex. It's a 4-nm hydroxyl dendrimer scaffold covalently linked to 7 to 8 sunitinib-analog VEGFR/PDGFR TKI molecules.¹⁹ The molecule is designed to cross the blood-retinal barrier following subcutaneous injection and selectively accumulate in activated microglia, macrophages and hypertrophic RPE within sites of choroidal neovascularization. The agent is renally cleared, which avoids the hepatic toxicity associated with oral TKIs.¹⁹ Interim 24-week Phase II data including 19 patients showed a 69-percent reduction in supplemental anti-VEGF injection burden in the nAMD cohort and 77 percent in the DME cohort. Among DME patients, mean BCVA improved by +4.5 letters and mean CST improved by -69 μ m at 24 weeks.²⁰ In the nAMD cohort specifically, a separate analysis of eight completing patients reported a 79.9-percent reduction in treatment burden, +3 BCVA letters and -45.5 μ m CST at 24 weeks.⁴

Safety considerations

No cases of severe intraocular inflammation, occlusive retinal vasculitis or endophthalmitis have been reported across the intravitreal TKI programs.³ Implant migration into the anterior chamber hasn't been observed in clinical trials to date for either Duravyu or Axpaxli. In contrast, topical TKI formulations have demonstrated dose-dependent corneal epitheliopathy. Long-term safety data beyond two years remain limited for all TKI modalities.

Bottom line

TKIs may offer sustained treatment of retinal vascular diseases. Between the SOL-1 readout and the upcoming SOL-R

**PAN-90806
(Zhaoke
Ophthalmology)
is a selective
inhibitor of
VEGF-receptor
signaling in
Phase II testing
as a once-daily
topical drop.**

and LUCIA results, patients may have more treatment options in the future. Suprachoroidal, periocular, topical and subcutaneous approaches may add further options but remain earlier in development. Future considerations include real-world durability against faricimab and aflibercept 8 mg treat-and-extend regimens, long-term safety beyond two years and performance in refractory disease. ^{RS}

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(Continued from page 17)

therapy “could be practice-changing.” An investigator posts photographs from an advisory-board dinner, comments that enrollment has gone exceptionally well or suddenly becomes unusually enthusiastic about a drug shortly before results are released. Before, those behaviors might primarily have raised questions about professionalism, promotion or disclosure. Now someone may literally put money behind what they think those signals mean.

The new standard can't simply be, “I didn't reveal the results.” Information leakage exists on a spectrum. Physicians routinely communicate enthusiasm, skepticism and confidence through conference remarks, podcasts, LinkedIn posts, X, Instagram, likes, reposts and private online groups. Individually, these signals may seem trivial. Collectively, they can become data.

Physicians involved in trials therefore need stricter boundaries. We can't trade contracts related to trials in which we participate. We can't discuss nonpublic observations about enrollment, efficacy or safety. More than ever we have to avoid even the vaguest hints about how a study appears to be progressing. We must be cautious about amplifying sponsor messaging while blinded results remain pending. Finally, we must disclose investigator, consulting and financial relationships when publicly discussing a therapy.

Sponsors and academic institutions should address this directly as well. Traditional confidentiality training was designed for an era in which leaking information meant handing someone a document or explicitly disclosing a result. Today, information may leak through a podcast aside, an emoji, a “like,” or an enthusiastic post from an investigator whose followers know exactly which study he's involved with.

Prediction markets have therefore created something medicine has not previously had to think much about: a direct financial price attached to the public perception of an unfinished clinical trial. A useful test may be straightforward: Would you be comfortable seeing your post displayed next to a live betting market for the trial, with traders changing their positions based partly on what they think your words imply? If the answer is no, it probably shouldn't be posted. Because once clinical trials become tradable events, a physician's social media activity may no longer be just commentary on the science: It can become part of the market itself. ^{RS}

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An 82-Year-Old Monocular Patient Concerned About Progression to Geographic Atrophy (GA)

Case Presentation

An 82-year-old female with a history of age-related macular degeneration (AMD) presented with increasing concerns regarding progressive vision loss in her only functional eye, following postoperative endophthalmitis in the fellow eye which resulted in hand-motion vision.

Despite her age, the patient remained highly active and independent. She enjoyed knitting, reading, driving, and using electronic devices, including her iPad. Over time, however, she became increasingly concerned about worsening vision and preserving function in her remaining seeing eye.

At an earlier visit, multimodal imaging demonstrated findings consistent with geographic atrophy (GA), although a formal diagnosis had not yet been established (Figure 1). When the patient returned with visual complaints one year and eight months later, it was apparent the GA had grown (Figure 2), and the patient was motivated to immediately start anti-complement therapy to slow the progression. After 12 months of therapy (Figure 4), visual acuity remained stable and FAF imaging showed minimal growth toward the fovea.

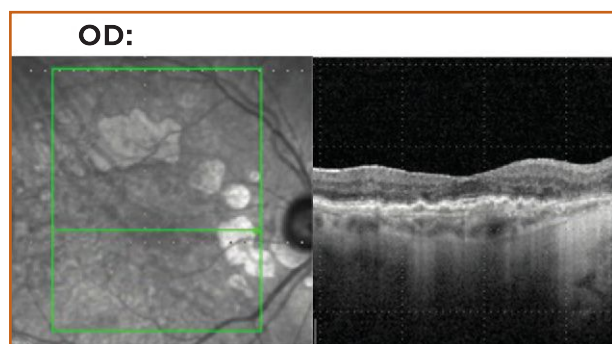


Figure 1. Baseline imaging demonstrated early areas of atrophy consistent with GA.

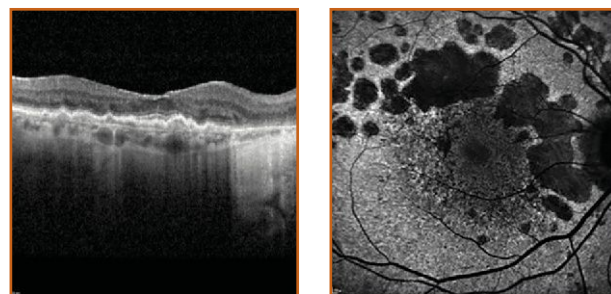


Figure 2. FAF and OCT at diagnosis revealed multifocal extrafoveal lesions with surrounding hyperautofluorescence and corresponding retinal atrophy.

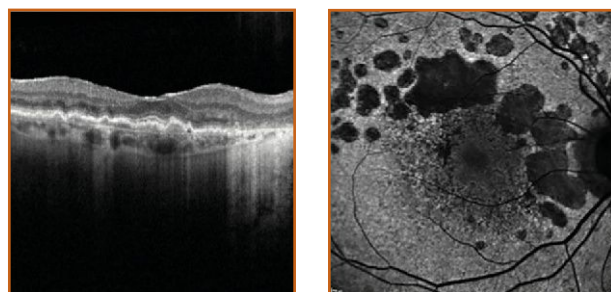


Figure 3. After six months of treatment, FAF and OCT imaging demonstrated minimal progression over time. Visual acuity was 20/30+2.

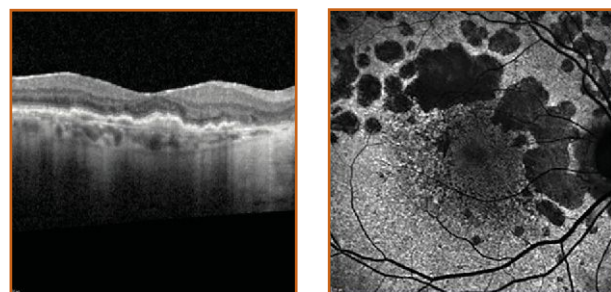


Figure 4. After 12 months of treatment, FAF and OCT imaging continued to demonstrate progression. Visual acuity was 20/25-3.



Would you have initiated treatment in this patient? Understand Dr. Sambhara's rationale.

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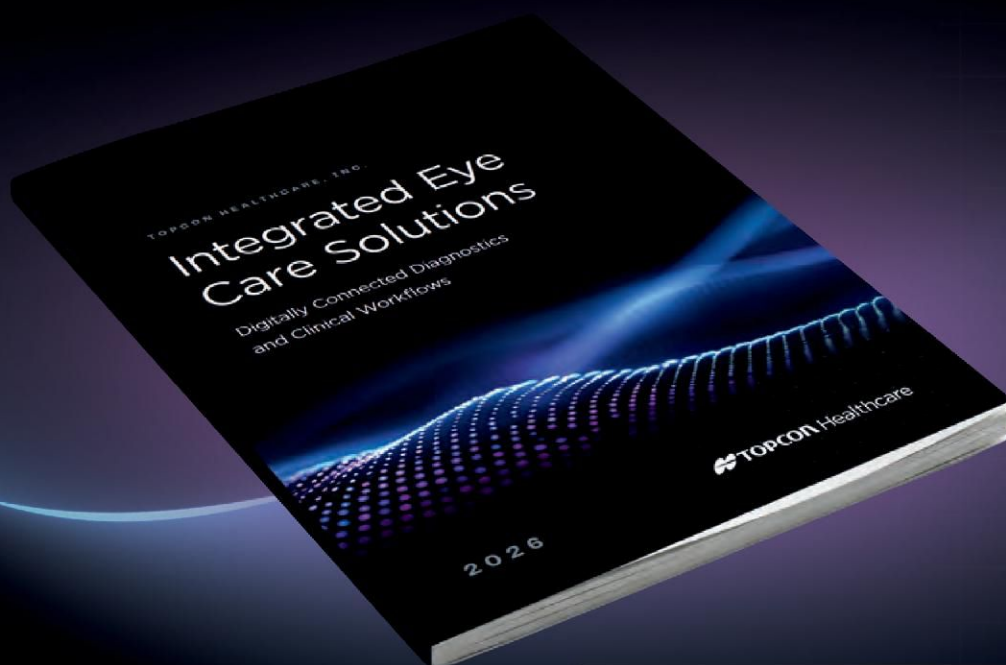
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