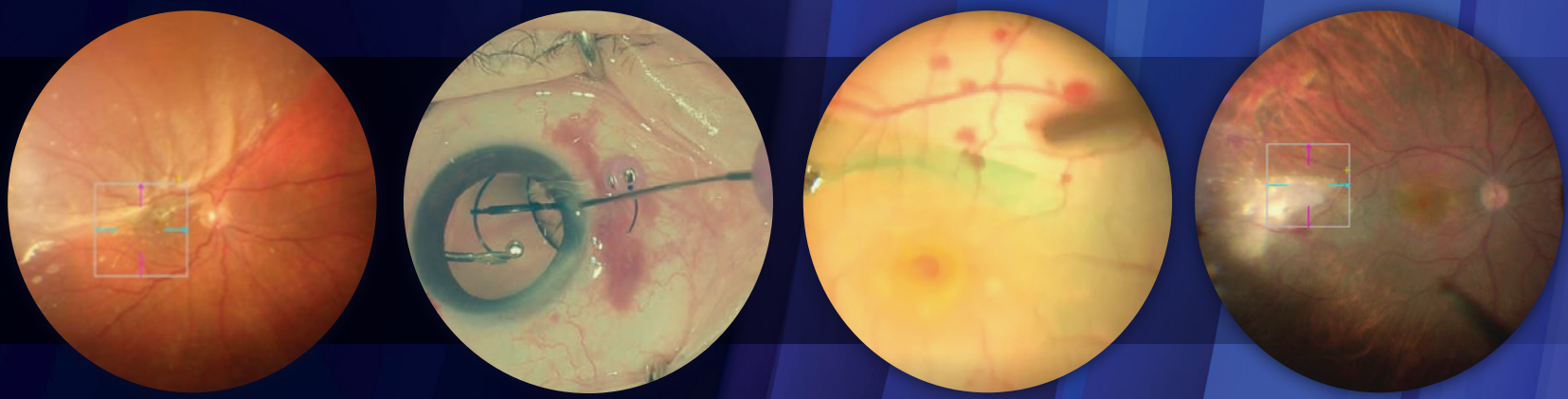
RT
Retina Today
JANUARY/FEBRUARY 2023 VOL. 18, NO. 1
RETINATODAY.COM

eyetube

# SURGICAL TECHNIQUES AND TECHNOLOGIES



Top surgeons share their go-to approaches and the latest tools reshaping the OR.

OPTIC DISC PIT MACULOPATHY TREATMENT OPTIONS | MASTER VITREORETINAL BIOPSIES | 10 TIPS FOR SUBRETINAL DELIVERY

IVERIC bio

# DEVELOPING TRANSFORMATIVE THERAPIES FOR RETINAL DISEASES

We are focused on developing treatments for patients suffering from retinal diseases with significant unmet medical needs.

**Geographic Atrophy** | **Stargardt Disease** | **Inherited Retinal Diseases**

Learn more at IvericBio.com

*Retina Today (ISSN 1942-1257) © 2023 Bryn Mawr Communications LLC is published January/February, March, April, May/June, July/August, September, October, and November/December by Bryn Mawr Communications LLC, 1008 Upper Gulph Road, Wayne, PA 19087. Subscription is free to all applicable US retina physicians. All others, applicable subscription charges apply. For subscription information call +1 800 492 1267 (US only) or e-mail retinatoday@bmctoday.com. Pending periodical postage paid at Wayne PA and additional entry offices. POSTMASTER Please send address changes to Bryn Mawr Communications LLC, 1008 Upper Gulph Road, Wayne, PA 19087. Bryn Mawr Communications LLC provides certain customer contact data, which may include customer names, addresses, phone numbers and e-mail addresses, to third parties for promotional and/or marketing purposes. If you do not wish Bryn Mawr Communications LLC to make your contact information available to third parties for any marketing purposes, please contact us at 800-492-1267 or e-mail us at retinatoday@bmctoday.com. This publication is intended for health care professionals and providers only. The information contained in this publication, including text, graphics and images, is for informational purposes only and is not intended to be a substitute for professional medical advice. Bryn Mawr Communications LLC, via its Editors and the Publisher, accepts no responsibility for any injury or damage to persons or property occasioned through the implementation of any ideas or use of any product described herein. While great care is taken by the Publisher and Editors to ensure that all information is accurate, it is recommended that readers seek independent verification of advice on drug or other product usage, surgical techniques and clinical processes prior to their use. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors, the publication or the Editorial Board. References made in articles may indicate uses of medical equipment or drugs at dosages, for periods of time and in combinations not included in the current prescribing information. Inclusion of advertising material in this publication, or in supplements thereof, does not constitute any representation or guarantee by Bryn Mawr Communications LLC of the quality of such products or of the claims made by the manufacturers.*

# A CAN-DO ATTITUDE


We have been talking a lot about how much our specialty has changed over the last few decades. In less than 20 years, we went from little to no therapeutics for our wet AMD and diabetic eye disease patients to a plethora of options—so many, in fact, that many of us have a bigger refrigerator on our wish lists.

With all the hubbub surrounding the rapidly expanding therapeutic landscape, it can be easy to overlook innovation in the OR. Today's surgical suite is significantly more high-tech with the advent of 3D heads-up displays, intraoperative OCT, smaller-gauge vitrectomy, and advanced tools. That's why we prefer to kick off the new year with an issue dedicated to our roots—surgery.

Don't get us wrong, these innovations are wonderful to have, but what matters most in the OR is the surgeon. With the right skillset and a willingness to think outside the box at times, surgeons can work wonders. We all love hearing success stories in which a patient faced with the possibility of blindness ends up with 20/40 vision postoperatively. When those cases are discussed at the podium, the presenter more often than not says something like, "I had heard about this technique from a colleague and decided to give it a try." That willingness to try new approaches is what hooked many of us in residency and fellowship.

Perhaps nowhere is this innovative mindset more apparent than with secondary IOLs and macular holes.

In this month's roundtable article (and podcast!), Christina Y. Weng, MD, MBA; Ashkan M. Abbey, MD; María H. Berrocal, MD; and Omesh P. Gupta, MD, MBA, discuss their preferred techniques for secondary IOL rescue/repair, as well as tips, tricks, and challenges. Note that they all have a *preferred* technique, and they all have tried each other's varied methods. None of them handle a secondary IOL in the exact same way, and yet all four of these surgeons have incredible outcomes. They are also tweaking their techniques as they go. Dr. Berrocal, for example, likes the modified Yamane technique, but she puts her own twist on it to save time and reduce both complications and surgical waste—what she likes to call the abbreviated modified Yamane.

The same can be said for macular hole surgery these days—no two patients are alike, and neither are our surgical approaches. Also in this issue, Sophie J. Bakri, MD, shares a rundown of the many ways we can treat macular holes, including internal limiting membrane flaps, autologous platelet-rich plasma, human amniotic membrane, macular hole plugging, autologous neurosensory retinal flaps, and macular buckling. The right treatment approach depends on each patient case and the surgeon's comfort with various techniques. These cases also push surgeons to try new methods and materials, particularly when a tried-and-true surgical approach just isn't getting the hole to close.

What makes these advances and updated surgical techniques so much fun (other than improving patient outcomes, of course) is the fact that we collaborate with each other to make them happen. We love to share success stories, examine intra- and postoperative complications, discuss new surgical approaches, and learn from each other. It's no surprise that we have so many meetings with surgical video contests, case-based sessions, and panels. If retina specialists are known for anything, it's that we are never afraid to expand our surgical armamentarium.

Look through this issue, and we can guarantee you will want to try a few of these tricks the next time you have a tough case in the OR. ■


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

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

## ALL THINGS MEDICAL

*Is medical retina your jam? We've got you covered! Check out these articles:*

**It Takes a Village to Make a Diagnosis**
Collaboration is crucial when you're stumped with a tough case.
By Cassie Ludwig, MD, and Nimesh A. Patel, MD

**Diagnosing and Managing Pediatric Retinal Vasculitis**
High-quality fundus imaging and aggressive treatment of inflammation is critical for children with retinal vasculitis.
By Dilraj Grewal, MD

**The Case of the Enormous Blind Spot**
Learn to diagnose acute idiopathic blind spot enlargement.
By Zurab Glonti, MD; Shalva Skhirtladze, MD; and Giorgi Mekvabishvili, MD

0.18 mg
YUTIQ®
(fluocinolone acetonide intravitreal implant) 0.18 mg

# Discover continuous calm in uveitis[1]

YUTIQ is designed to deliver a sustained release of fluocinolone for up to 36 months for patients with chronic non-infectious uveitis affecting the posterior segment of the eye[1]

- Proven to reduce uveitis recurrence at 6 and 12 months[1]*
  At 6 months–18% for YUTIQ and 79% for sham for Study 1 and 22% for YUTIQ and 54% for sham for Study 2 (*P*<.01). At 12 months–28% for YUTIQ and 86% for sham for Study 1 and 33% for YUTIQ and 60% for sham for Study 2.
- Extended median time to first recurrence of uveitis[1,2]
  At 12 months–NE† for YUTIQ/92 days for sham in Study 1; NE for YUTIQ/187 days for sham in Study 2.
- Mean intraocular pressure (IOP) increase was comparable to sham[1,2]
  Study was not sized to detect statistically significant differences in mean IOP.

For more information, visit **YUTIQ.com**

*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, Phase 3 studies in adult patients (N=282) with non-infectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to non-infectious uveitis, or the need for rescue medications.

†NE=non-evaluable due to the low number of recurrences in the YUTIQ group.

## INDICATIONS AND USAGE

**YUTIQ®** (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

**Ocular or Periocular Infections:** YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

**Hypersensitivity:** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

### WARNINGS AND PRECAUTIONS

**Intravitreal Injection-related Effects:** Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

**Steroid-related Effects:** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

**Risk of Implant Migration:** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

### ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

**Please see brief summary of full Prescribing Information on adjacent page.**

**References: 1.** YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full US Prescribing Information. EyePoint Pharmaceuticals, Inc. May 2021. **2.** Data on file.

EYEPOINT® PHARMACEUTICALS


480 Pleasant Street, Suite B300, Watertown, MA 02472
08/2021
US-YUT-2100061

**YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection**
**Initial U.S. Approval: 1963**

**BRIEF SUMMARY: Please see package insert for full prescribing information.**

**1. INDICATIONS AND USAGE.** YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

**4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections.** YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

**5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects.** Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

**6. ADVERSE REACTIONS. 6.1. Clinical Studies 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 associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

**Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients**

| Ocular | | |
|---|---|---|
| **ADVERSE REACTIONS** | **YUTIQ (N=226 Eyes) n (%)** | **Sham Injection (N=94 Eyes) n (%)** |
| Cataract[1] | 63/113 (56%) | 13/56 (23%) |
| Visual Acuity Reduced | 33 ( 15%) | 11 (12%) |
| Macular Edema | 25 ( 11%) | 33 (35%) |
| Uveitis | 22 ( 10%) | 33 (35%) |
| Conjunctival Hemorrhage | 17 ( 8%) | 5 ( 5%) |
| Eye Pain | 17 ( 8%) | 12 (13%) |
| Hypotony Of Eye | 16 ( 7%) | 1 ( 1%) |
| Anterior Chamber Inflammation | 12 ( 5%) | 6 ( 6%) |
| Dry Eye | 10 ( 4%) | 3 ( 3%) |
| Vitreous Opacities | 9 ( 4%) | 8 ( 9%) |
| Conjunctivitis | 9 ( 4%) | 5 ( 5%) |
| Posterior Capsule Opacification | 8 ( 4%) | 3 ( 3%) |
| Ocular Hyperemia | 8 ( 4%) | 7 ( 7%) |
| Vitreous Haze | 7 ( 3%) | 4 ( 4%) |
| Foreign Body Sensation In Eyes | 7 ( 3%) | 2 ( 2%) |
| Vitritis | 6 ( 3%) | 8 ( 9%) |
| Vitreous Floaters | 6 ( 3%) | 5 ( 5%) |
| Eye Pruritus | 6 ( 3%) | 5 ( 5%) |
| Conjunctival Hyperemia | 5 ( 2%) | 2 ( 2%) |
| Ocular Discomfort | 5 ( 2%) | 1 ( 1%) |
| Macular Fibrosis | 5 ( 2%) | 2 ( 2%) |
| Glaucoma | 4 ( 2%) | 1 ( 1%) |
| Photopsia | 4 ( 2%) | 2 ( 2%) |

(continued)

**Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients**

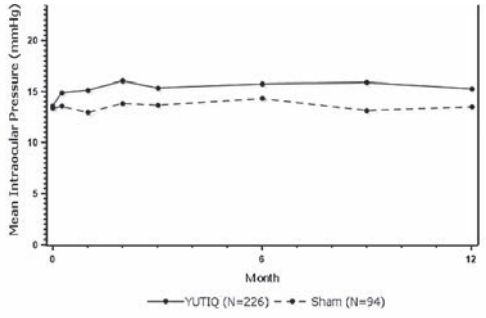
| Ocular | | |
|---|---|---|
| **ADVERSE REACTIONS** | **YUTIQ (N=226 Eyes) n (%)** | **Sham Injection (N=94 Eyes) n (%)** |
| Vitreous Hemorrhage | 4 ( 2%) | 0 |
| Iridocyclitis | 3 ( 1%) | 7 ( 7%) |
| Eye Inflammation | 3 ( 1%) | 2 ( 2%) |
| Choroiditis | 3 ( 1%) | 1 ( 1%) |
| Eye Irritation | 3 ( 1%) | 1 ( 1%) |
| Visual Field Defect | 3 ( 1%) | 0 |
| Lacrimation Increased | 3 ( 1%) | 0 |
| **Non-ocular** | | |
| **ADVERSE REACTIONS** | **YUTIQ (N=214 Patients) n (%)** | **Sham Injection (N=94 Patients) n (%)** |
| Nasopharyngitis | 10 ( 5%) | 5 ( 5%) |
| Hypertension | 6 ( 3%) | 1 ( 1%) |
| Arthralgia | 5 ( 2%) | 1 ( 1%) |

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

**Table 2: Summary of Elevated IOP Related Adverse Reactions**

| ADVERSE REACTIONS | YUTIQ (N=226 Eyes) n (%) | Sham (N=94 Eyes) n (%) |
|---|---|---|
| IOP elevation ≥ 10 mmHg from Baseline | 50 (22%) | 11 (12%) |
| IOP elevation > 30 mmHg | 28 (12%) | 3 (3%) |
| Any IOP-lowering medication | 98 (43%) | 39 (41%) |
| Any surgical intervention for elevated IOP | 5 (2%) | 2 (2%) |

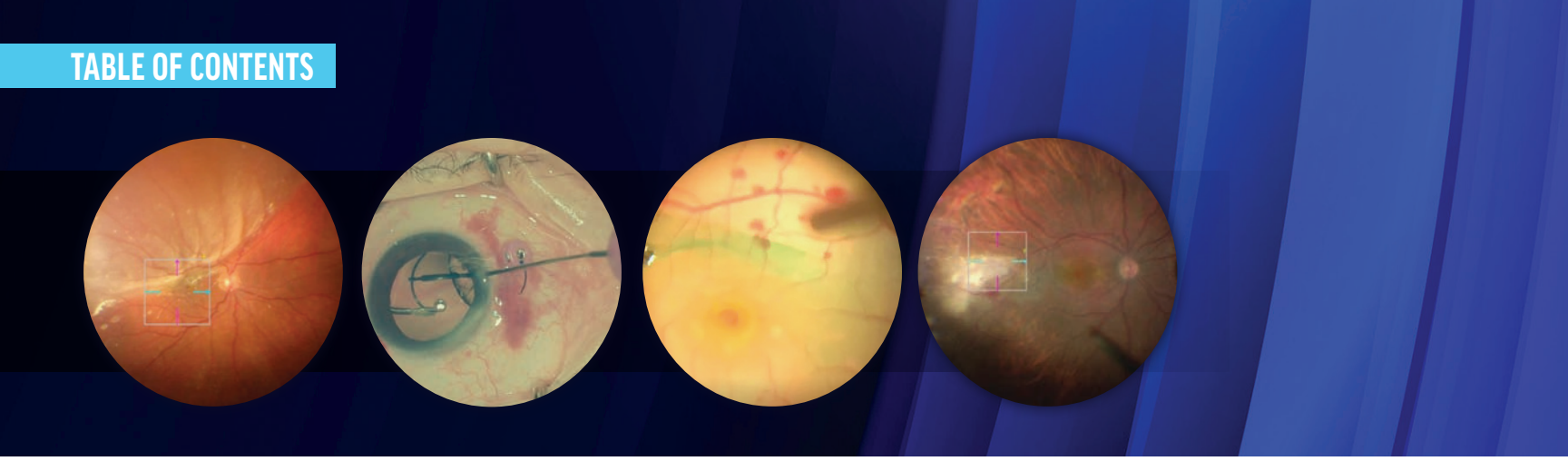
**Figure 1: Mean IOP During the Studies**




**8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy.** Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Manufactured by:
EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA
Patented.

# TABLE OF CONTENTS



Cover image credit: ©iStockphoto.com


26 **Tackle Secondary IOLs With Ease**
A conversation with Christina Y. Weng, MD, MBA; Ashkan M. Abbey, MD; María H. Berrocal, MD; and Omesh P. Gupta, MD, MBA

30 **Macular Hole Surgery Roundup**
By Sophie J. Bakri, MD

32 **Optic Disc Pit Maculopathy: Today's Treatment Options**
By Daniel Su, MD, and David Boyer, MD

34 **10 Tips for Subretinal Delivery**
By Ninel Z. Gregori, MD

38 **Five Ways iOCT Can Enhance Vitreoretinal Surgery**
By Leanne M. Clevenger, MD, and Aleksandra V. Rachitskaya, MD, FASRS

42 **Master the Vitreoretinal Biopsy Basics**
By Abel Hamdan, MD; Danny A. Mammo, MD; and Sunil K. Srivastava, MD

46 **Chromovitrectomy: A Primer**
By Parnian Arjmand, MD, MSc, FRCSC, DABO


## DEPARTMENTS


**UP FRONT**
4 **Medical Editors' Page**
8 **Retina News**
14 **One To Watch: Mohsin H. Ali, MD**

**MEETING MINUTES**
12 **Imaging Pearls at ARDS 2022**
By Rebecca Hepp, Editor-in-Chief

**PEDIATRICS**
15 **Diagnosing and Managing Pediatric Retinal Vasculitis**
By Dilraj S. Grewal, MD

**MEDICAL RETINA**
18 **It Takes a Village to Make a Diagnosis**
By Cassie Ludwig, MD, and Nimesh A. Patel, MD

**GLOBAL PERSPECTIVES**
22 **Pneumatic Retinopexy: Common Myths Dispelled**
By Mohammed Al-Falah, MD, FRCSC; Rajeev H. Muni, MD, MSC, FRCSC; and Peter J. Kertes, MD, FRCSC

**CODING ADVISOR**
49 **Debunking Common Retina Coding Myths**
By Joy Woodke, COE, OCS, OCSR

**FELLOWS' FOCUS**
52 **Identifying AMD Overlap Syndromes**
By Saagar Pandit, MD, MPH; Asad F. Durrani, MD; Anand Gopal, MD; and Linnet Rodriguez, MD

**VISUALLY SPEAKING**
56 **The Case of the Enormous Blind Spot**
By Zurab Glonti, MD; Shalva Skhirtladze, MD; and Giorgi Mekvabishvili, MD

**IN THE BACK**
48 **Rising Stars in Retina: Meera D. Sivalingam, MD**
58 **Ad Index**


**ONLINE EXCLUSIVE:**
**5 Questions with Robyn Guymer AM, MBBS, PhD, FRANZCO, FAHMS**

JANUARY/FEBRUARY 2023
VOL. 18, NO. 1 | RETINATODAY.COM

# CAROL L. SHIELDS, MD, RECEIVES HIGHEST NCAA HONOR

Carol L. Shields, MD, chief of the Ocular Oncology Service at Wills Eye Hospital in Philadelphia, was named the 2023 recipient of the annual Theodore Roosevelt Award of the National Collegiate Athletic Association (NCAA). This award is the highest honor that the NCAA confers.[1]

Dr. Shields has achieved worldwide renown in ophthalmology, with more than 700 lectures on such topics as retinoblastoma, uveal melanoma, and other malignancies, as well as more than 1,400 journal publications.[2] She has been recognized many times for achievements in the field, including appearing in the 2014 and 2016 Ophthalmology Top 100 Power List, and earning such accolades as the Netherlands Ophthalmological Society Donders Award and the AAO's Life Achievement Award. She was also the first elected President of the International Society of Ocular Oncology.

Dr. Shields' athletic legacy is perhaps less well known in the retina community but has certainly left a significant impression on women in sports today, as this latest award demonstrates. She was not planning to play basketball at the collegiate level when she started school at the University of Notre Dame in 1975, but she ultimately decided to join the team. It was only the fourth year that the university admitted women to attend at all. During her basketball career, Dr. Shields was named co-captain three times, and she became the first woman to receive Notre Dame's Byron V. Kanaley Award for excellence in athletics and academics.

These athletic achievements in the early days of Title IX and her professional accolades laid the groundwork for generations of women who have followed to enjoy more opportunities to lead successful, well-rounded careers. The "Teddy" Award, as it is nicknamed, was presented to Dr. Shields at the NCAA Honors Celebration on January 11, 2023.

1. Myers M. 2023 Theodore Roosevelt Award: Dr. Carol Lally Shields. NCAA. December 7, 2022. Accessed December 21, 2022. www.ncaa.org/news/2022/12/7/media-center-2023-theodore-roosevelt-award-dr-carol-lally-shields.aspx
2. 2012 Silver Medalist Carol L. Shields, MD, Biography. AAPOS. Accessed December 22, 2022. aapos.org/meetings/lectures/hall-of-fame/silver-medalists/carol-shields

## SIMPLIFIED OPTORETINOGRAPHY TECHNIQUE COULD SAVE DIAGNOSTIC TIME

A new optoretinography technique could make measuring retinal function easier and faster, according to researchers at the University of California, Davis. This approach, termed *velocity-based optoretinography*, measures the velocity at which the retinal neurons move in relation to each other—and avoids the need to resolve and track individual neurons.[1]

"We believed that even if the positions of the features vary from cell to cell, the speed at which they move relative to one another would be highly correlated among cells," said team leader Ravi Jonnal, PhD.[2]

To test this theory, the researchers developed a new OCT camera that uses a single operator to retrieve images from more retina locations than otherwise possible. Jonnal and his colleagues collected measurements from three healthy volunteers, achieving results within 15 minutes.

1. Vienola KV, Valente D, Zawadzki RJ, Jonnal RS. Velocity-based optoretinography for clinical applications. *Optica*. 2022;9(10):1100-1108.
2. New imaging technique could speed up development of eye disease treatments [press release]. Optica Publishing Group. September 19, 2022. Accessed January 10, 2023. www.optica.org/en-us/about/newsroom/news_releases/2022/september/new_imaging_technique_could_speed_up_development_o/

## STUDY SHOWS CNV IS COMMON IN BEST VITELLIFORM MACULAR DYSTROPHY

Researchers at the University of Iowa have found that choroidal neovascularization (CNV) is common in Best vitelliform macular dystrophy (BVMD), including in the early stages of the disease. The study used swept-source OCT angiography to accomplish three objectives: evaluate the prevalence of CNV in BVMD, identify structural features associated with CNV, and provide insight into the role of CNV in vitelliform lesion evolution.[1] The team, led by Ian C. Han, MD, also noted that "the presence of focal choroidal excavations or nodular pillars should heighten clinical suspicion for CNV, which may accelerate vitelliform lesion evolution."[1]

The study included a total of 53 eyes (27 patients) with molecularly-confirmed BVMD. Of these eyes, the researchers identified CNV in 50.9% and found that 63.0% of those with CNV had a vitelliform (Gass stage 2) lesion. Additional study results included the identification of other structural features associated with CNV such as choroidal excavations and nodular pillars.

1. Han IC, Coussa RG, Mansoor M, et al. Choroidal neovascularization is common in Best vitelliform macular dystrophy and plays a role in vitelliform lesion evolution [preprint published online December 13, 2022]. *Ophthalmol.*

SYFOVRE™
(pegcetacoplan) injection

## Coming Soon

# Get Ready

## Something new is on the way

Scan to sign up for updates or visit www.SyfovreECP.com today

Apellis

## Updates From Eyewire+

- **Harrow** is to acquire five ophthalmic products from Novartis for $175 million, including nepafenac ophthalmic suspension 0.3% (Ilevro), nepafenac ophthalmic suspension 0.1% (Nevanac), moxifloxacin hydrochloride ophthalmic solution 0.5% (Vigamox), dexamethasone ophthalmic suspension 0.1% (Maxidex), and triamcinolone acetonide injectable suspension 40 mg/ml (Triesence). Novartis will continue to sell these products during an estimated 6-month transfer period and will turn these profits over to Harrow. After this period, Harrow will assume all US market activities, while Novartis retains the rights to them outside of the United States.
- The FDA granted orphan drug designation to **Ocugen's** human nuclear hormone receptor subfamily 2 group E member 3 (OCU400), a novel therapy under investigation for the treatment of retinitis pigmentosa and Leber congenital amaurosis. OCU400 targets nuclear hormone receptors, which play a regulatory role in various processes such as homeostasis, reproduction, development, and metabolism.
- **Oxurion** announced that an Independent Data Monitoring Committee has recommended that the company continue its phase 2b clinical trial of investigational plasma kallikrein candidate (THR-149) for the treatment of patients with diabetic macular edema who have experienced a suboptimal response to anti-VEGF therapy.
- **Lineage Cell Therapeutics** announced that its partner, **Genentech**, launched a phase 2a multicenter, open-label, single-arm study of RG6501 (OpRegen), an investigative retinal pigment epithelium cell therapy for the treatment of geographic atrophy. The goals of this study are to optimize subretinal delivery and evaluate the safety and adverse events profile at 3 months postoperative.
- **Apellis Pharmaceuticals** submitted a Marketing Authorization Application to the European Medicines Agency for its investigational, targeted C3 complement therapy, intravitreal pegcetacoplan. Apellis is also awaiting the US FDA's decision regarding the approval of pegcetacoplan, with a Prescription Drug User Fee Act target action date of February 26.
- The European Medicines Agency recently validated **Outlook Therapeutics'** Marketing Authorization Application for ONS-5010 (Lytenava, bevacizumab-vikg), an investigational ophthalmic formulation of bevacizumab for the treatment of wet AMD. The estimated decision date is expected in early 2024.
- **Iveric Bio** announced that it has completed submission of the final part of its new drug application (NDA) for avacincaptad pegol, which is under rolling review by the FDA. The final portion of this submission included data on chemistry, manufacturing, and controls.

Check out *Eyewire+* for more of the latest news in retina.

## BIOSIMILAR IMMUNOGENICITY AND SAFETY CONCERNS MAY BE UNWARRANTED

In a post hoc analysis of a randomized equivalence trial, Bressler et al investigated the association between the immunogenicity of the ranibizumab biosimilar SB11 (Byooviz, Samsung Bioepis/Biogen) and efficacy, safety, and pharmacokinetics.[1] The analysis examined a randomized, double-masked, parallel-group phase 3 equivalence study.

The researchers found that the incidence of antidrug antibodies was low for ranibizumab biosimilar products, and there were no statistical or clinically significant differences for either BCVA or central subfield thickness among study patients with and without antidrug antibodies. In addition, the drug's immunogenicity didn't have a clinically relevant association with efficacy, safety, or pharmacokinetic profiles.

In the paper's conclusion, the authors noted that their findings suggest that certain concerns about the immunogenicity and overall safety of the ranibizumab biosimilar "do not appear warranted at this time, although routine pharmacovigilance monitoring remains warranted."

1. Bressler NM, Kim T, Oh I, Russo P, Kim MY, Woo SJ. Immunogenicity with ranibizumab biosimilar SB11 (Byooviz) and reference product lucentis and association with efficacy, safety, and pharmacokinetics: a post hoc analysis of a phase 3 randomized clinical trial [preprint published online December 15, 2022]. *JAMA Ophthalmol*.

## TREATMENT APPROACH NOT ASSOCIATED WITH TRD RISK IN PDR

In a case-controlled study of 1,192 adults, Tsui et al found that stand-alone treatment with anti-VEGF injection for proliferative diabetic retinopathy (PDR) was not associated with an increased risk of tractional retinal detachment (TRD) compared with laser only or combination laser/anti-VEGF injection.[1] After matching 214 patients with PDR and TRD with 978 controls with PDR only, the researchers found no difference in the odds of TRD for those treated with injection only compared with patients who received laser only. The analysis did reveal that patients who received the combination of laser and anti-VEGF injection had higher odds of TRD compared with those who received only laser; patients who received no treatment had lower odds of TRD.

Results of the analysis also found no increased risk of TRD with a 6-month or longer period of loss to follow-up (LTFU) compared with patients with no LTFU. However, the researchers also warned that LTFU rates "continue to remain high in patients with PDR, which can contribute to substantial vision loss regardless of treatment regimen." ■

1. Tsui JC, Yu Y, VanderBeek BL. Association of treatment type and loss to follow-up with tractional retinal detachment in proliferative diabetic retinopathy [preprint published online December 1, 2022]. *JAMA Ophthalmol*.

THE GOLD-STANDARD OF PATTERN SCANNING LASER TECHNOLOGY HAS ADVANCED TO THE NEXT LEVEL.

# IRIDEX® PASCAL®


## CLINICAL VERSATILITY WITH PROVEN POWER

Now, the efficiency and convenience of the Iridex PASCAL Laser System is available with MicroPulse®, the world's leading tissue-sparing ophthalmic laser therapy.

LEARN MORE ABOUT THE IRIDEX ADVANTAGE FOR YOUR PRACTICE

www.iridexretina.com

IRIDEX®

# IMAGING PEARLS AT ARDS 2022

Experts discussed the latest advances in OCT imaging.

BY REBECCA HEPP, EDITOR-IN-CHIEF

*The novel therapeutics that are pouring out of the pipeline may be taking center stage lately, but we all know that imaging technology has seen just as much growth—and may be just as important. During our 50th annual Aspen Retinal Detachment Society (ARDS) meeting, two experts—K. Bailey Freund, MD, and Judy E. Kim, MD, FARVO, FASRS—shared their insights into the newest imaging modalities and techniques that may change how we care for our patients.*

*If imaging is in your wheelhouse, don't miss the 2023 Taylor Smith & Victor Curtin Lecture on advances in retinal imaging, which will be presented by Giovanni Staurenghi, MD.*

**— Timothy G. Murray, MD, MBA, FASRS**

## INSIGHTS ON HIGH-RESOLUTION OCT

Dr. Freund began his lecture with a quick review of high-resolution OCT—a prototype that increases the axial resolution (but not lateral resolution) to 3 µm. The increased resolution provides a much better definition of the outer retinal bands than current OCT models; in fact, "if we have a patient who is young and has very clear media, we can now make out six outer retinal bands," according to Dr. Freund. Researchers can see every single capillary, he added. The device can also provide dense raster scans with a 6-µm inter-scan distance—"with exquisite detail"—and provides OCT angiography, he added.

Dr. Freund then focused on specific clinical indications for which high-resolution OCT has proven useful for him. First up was a patient with new lacquer cracks and small hemorrhages. The details of the scan helped Dr. Freund be confident that the patient did not have any neovascularization.

Dr. Freund noted that he has a particular interest in pseudoxanthoma elasticum and angioid streaks, and he showed how high-resolution OCT could help to explain why some streaks are red and some have hypopigmented areas—the retinal pigment epithelium (RPE) bridges the gap in areas that are red but not in the hypopigmented areas.

Dr. Freund also sees an important role for this high-resolution imaging tool with new therapies on the way for dry AMD. "Once we get into the phase where we have complement inhibition, the deposition of material between the RPE and Bruch membrane, whether it's basal laminar deposits or other materials, will become a very important indicator to help us determine which patients might be suitable for complement inhibitors," he explained. High-resolution OCT can do that, he said.

Another pearl he wanted to emphasize using high-resolution OCT is that not every double-layer sign indicates neovascularization. He showed several examples of double-layer signs that were not traditional macular atrophy (such as acquired vitelliform lesions) to drive home the point.

Dr. Freund introduced a batch of clinical cases to help illustrate the many disease states that may benefit from high-resolution OCT imaging, including Best disease, extensive macular atrophy with pseudodrusen, bacillary layer detachment, choroideremia, persistent plaque-like maculopathy, macular telangiectasia type 2, solitary idiopathic choroiditis, and Stargardt, to name only a few.

## THE HISTOLOGY OF RETINAL IMAGING

In Dr. Freund's second ARDS lecture, he shared his takeaway right out of the gate: "histologic analysis of well-documented eyes could validate recent imaging technology and inform current and future treatments for AMD." To support this notion, he discussed imaging findings in three AMD subtypes, beginning with type 1 macular neovascularization.

Using multimodal imaging and AMD classifications, Dr. Freund and others have found evidence to suggest that type 1 neovascularization "appeared to have the potential to exert a protective effect on the overlying RPE and photoreceptors, providing some resistance to macular atrophy." Dr. Freund's team further suggested that treatment strategies could be altered to try to preserve type 1 neovascularization, which might help maintain central vision.

To learn more about and register for the 2023 ARDS meeting, set for March 4–8, visit aspenretina.com.

For one patient, long-term follow-up with OCT angiography showed significant atrophy in one eye with dry AMD over a span of 5 years; the fellow eye maintained vision because the atrophy continued to spare the area with type 1 neovascularization. "If we can figure out how to harness this naturally protective process and control these vessels, we will have found the cure for AMD," he speculated.

Moving on, he noted that basal laminar deposits and basal linear deposits are the two main histologic features that define the early and intermediate stages of AMD—or type 2 neovascularization. He walked attendees through several cases, including OCT imaging of a large drusenoid pigment epithelial detachment (PED) with an overlying vitelliform lesion. He highlighted the basal laminar deposit, a thin hyperreflective line beneath the RPE band and above the basal linear deposit that formed the drusenoid PED. He also emphasized that the basal laminar deposit can resemble a double-layer sign or a shallow, regular RPE elevation that you might think harbors neovascularization—but it doesn't.

As for type 3, Dr. Freund gave all the credit to Mary Elizabeth Hartnett, MD, FACS, FARVO, who helped the field understand the mechanisms behind type 3 macular neovascularization. "Once you lose the photoreceptors and the RPE, the Müller cells become activated, and they send processes down that start to invade that basal laminar deposit, forming a strong adhesion between what's left of the outer retina and this resilient basal laminar deposit material," he explained. A handful of cases later, the audience was well-versed on classic forms of type 3 neovascularization as well as atypical lesions that "can look identical to type 3, but are probably not true neovascular lesions," Dr. Freund concluded.

## ARTIFICIAL INTELLIGENCE AND RETINAL IMAGING

Dr. Kim began her talk by clarifying for the audience that they have all interacted with artificial intelligence (AI), whether they knew it or not; email, texting, facial recognition, and even ride shares all incorporate some form of AI, she noted.

"The field of medicine is leading AI," she continued. "Radiology, dermatology, pathology, ophthalmology—they all have imaging in common, and AI loves imaging."

She flashed a fundus photo on the screen, and no one in the audience could determine the patient's sex, age, or other demographics. But AI could, according to Dr. Kim. AI determined that the patient was female, a nonsmoker, and in the ballpark of 59 years of age. "Why should ophthalmologists be interested in this technology at all?" Dr. Kim queried. Because diabetes is an epidemic, and half of the patients remain undiagnosed, she explained.

AI can even interpret OCT images, she said. She provided an example of images segmented by layers and graded by human graders and AI, noting that the AI tools can tell if fluid is subretinal, foveal, or parafoveal, and even measure the volume. Home-based AI-powered OCT may also one day allow clinicians to track minute changes before and after injections, she said.

WATCH IT NOW


Clinical Insights from High-Resolution OCT

"We can find out how the fluid behaves between visits, which may help us to address undertreatment," she said. "We may have better visual acuity outcomes and decreased treatment burden because the patients can come in only when they accumulate a certain amount of fluid."

AI also can help with AMD. One day, this tool may be able to tell if the patient requires an urgent or routine referral, according to Dr. Kim, and it can predict conversion in early AMD, how the AMD will progress, how geographic atrophy will grow over time, and how many injections the patient may need.

But nothing is ever that easy, she cautioned. Ethics play a big part in AI implementation, and while AI doesn't have emotion, it can still introduce bias into the interpretation. The output is only as good as the data you provide—"garbage in, garbage out," Dr. Kim quipped. For example, if you put in data only from women or Caucasians, AI cannot provide a reliable interpretation of data from men or a Latinx patient.

"It's really, really important to have great data," she warned. Researchers need more data sets that are diverse, that include various races, ages, and genders, she added. Not only that, who is ultimately responsible if the machine misdiagnoses the patient? That is a question researchers will have to answer before AI truly can be embraced in clinical practice, she said.

"Right now, you have more power at your fingertips than entire generations that came before you," Dr. Kim said to wrap up. "That's what technology really is—it's possibility, adaptability, and capability. But in the end, it's only a tool. It's not about what technology can do, it's about what you can do with it." ■

RT Retina Today

# ONE TO Watch

Supported by

Allergan an AbbVie company

## WHERE IT ALL BEGAN

Mohsin H. Ali, MD, was born in Hyderabad, a large city in the south of India famous for its biryani, pearls, diamonds, and tech sector—though many ophthalmologists recognize it as the home of the L.V. Prasad Eye Institute. A few years later, his family moved to Kuwait, and a well-timed family vacation allowed everyone to escape the Kuwait invasion during the Gulf War. In the United States, his family settled near Wilmington, Delaware, where Dr. Ali spent most of his childhood. While growing up, he always knew that he wanted to be a physician like his father and so many others he admired.

Unsurprisingly, he enrolled in a BS/MD program at Jefferson Medical College in Philadelphia and completed his ophthalmology residency at the University of Illinois and Illinois Eye and Ear Infirmary in Chicago. He attended Duke University in Durham, North Carolina, for his vitreoretinal surgery fellowship, and he now lives in Northern Virginia (in his wife's hometown) with his wonderful wife, two sons, and baby daughter.

**Dr. Ali's Advice:**
**Choose a practice where you can surround yourself with colleagues you respect and admire and whose company you enjoy, and choose a location that is good for your family. Everything else will fall into place.**

## THE PATH TO RETINA

Dr. Ali's journey to the field of retina began the first time he looked through the OR microscope during a pars plana vitrectomy. He was mesmerized by the beauty, intricacy, and challenge of surgery in the posterior segment of the eye. Of course, being surrounded by the exemplary retina, uveitis, and oncology faculty and retina fellows during residency was just as influential—after all, many people tend to follow in the footsteps of those they greatly admire.

## SUPPORT ALONG THE WAY

Dr. Ali's father is a gastroenterologist, his mother is a teacher, and his older sister is an ophthalmologist. He likes to think that he has followed in each of their footsteps. They have been his first, and most significant, mentors. He has also been deeply influenced by mentors during his glaucoma research fellowship, attendings in residency, every one of his attendings and co-fellows in fellowship, and his colleagues in his current practice.

## AN EXPERIENCE TO REMEMBER

About a year after starting as an attending at the Retina Group of Washington, Dr. Ali was in the OR for several hours performing a retinal detachment repair on a severe post-traumatic retinal detachment with extensive proliferative vitreoretinopathy. He reflected on the second-year fellow he was working with, who at first struggled to perform a basic core vitrectomy but was now performing this advanced surgery with ease. Witnessing this transformation, Dr. Ali was filled with gratitude toward his own mentors for the patience and encouragement they similarly showed him during training. He was also filled with gratitude that he was now able to teach another generation of fellows to handle even the most complex surgical scenarios. From looking through the teaching scope as a resident and being mesmerized by vitreoretinal surgery to looking through the scope as a teacher, he had finally come full circle. ■

**Mohsin H. Ali, MD,** is a vitreoretinal surgeon at the Retina Group of Washington, located in and around the Washington, DC, metropolitan area. He mainly cares for adult patients with vitreoretinal diseases. He also trains vitreoretinal surgery fellows and teaches Georgetown ophthalmology residents and medical students. He is on the advisory board for Alimera and Allergan/AbbVie. He can be reached at **mali@rgw.com.**

# DIAGNOSING AND MANAGING PEDIATRIC RETINAL VASCULITIS

High-quality fundus imaging and aggressive treatment of inflammation is critical for children with retinal vasculitis.

BY DILRAJ S. GREWAL, MD

Pediatric uveitis is relatively uncommon, with a prevalence of 30 in 100,000 children and accounting for only 5% to 10% of all uveitis cases.[1,2] However, the vision-threatening complications are disproportionately higher, and up to 25% of children can progress to a VA of 20/200 or worse due to cataracts, ocular hypertension, glaucoma, macular edema, and amblyopia. Thus, ocular inflammation must be treated aggressively to prevent the occurrence of these ocular sequelae.

Unfortunately, pediatric uveitis can be challenging to manage because of the often delayed diagnosis, chronic course, examination difficulties, and side effects of medical treatment. It is also usually idiopathic, accounting for 30% to 50% of cases.[3] The pearls included in this article can help you to catch this condition early and treat it appropriately.

## THE CRITICAL IMAGING TOOL

The advent of widefield imaging systems has improved our ability to obtain high-quality fundus imaging in children, even in-office and without the use of anesthesia. While multimodal imaging—including fundus photography, OCT, and OCT angiography (OCTA)—is important, fluorescein angiography (FA) remains the critical tool for diagnosing and monitoring retinal vasculitis.[4-7]

The benefits of obtaining FA in children outweigh the logistical concerns, as FA provides substantial additional information beyond what the clinical examination can find. Nearly 80% of children with posterior uveitis deemed quiescent based on their clinical examination demonstrate persistent subclinical inflammation on FA that requires further treatment with immunomodulatory therapy (IMT) to obtain full disease control and true quiescence.[8]

Physicians may use oral fluorescein when venous access for FA is not feasible in a child. However, oral FA images are not directly comparable with intravenous FA images and may not be suitable for detecting subtle inflammation, particularly for peripheral findings in the later (10- to 20-minute) phases.

**AGGRESSIVE AND ADEQUATE TREATMENT OF OCULAR INFLAMMATION IS CRITICAL TO OPTIMIZE LONG-TERM VISUAL OUTCOMES IN CHILDREN WITH RETINAL VASCULITIS.**

Failing to identify and adequately control occult retinal vasculitis may contribute to the higher incidence of long-term complications in children with intermediate, posterior, or panuveitis and to the subsequent poorer prognosis compared with patients whose disease is isolated to the anterior segment.

## WHAT TO LOOK FOR

According to the Standardization of Uveitis Nomenclature Working Group, the presence of perivascular sheathing and vascular leakage or occlusion on a fundus FA may be used for the classification of retinal vasculitis.[9] Retinal vasculitis can be accompanied by retinal vascular sheathing, leakage, occlusion, or neovascularization. Features of active inflammation seen on FA include perivascular staining (venous or arterial), peripheral capillary leakage, late optic disc staining, peripheral retinal nonperfusion, and angiographic cystoid macular edema (Figure 1). In eyes apparently quiescent based on a dilated examination, 79% had FA activity.[8] Almost 80% of pediatric patients with idiopathic uveitis show some manifestations of retinal vasculitis, which is associated with a lower probability of inflammation control at 1 year, resulting in a worse visual prognosis.[10]

When performing FA, it is important to capture the

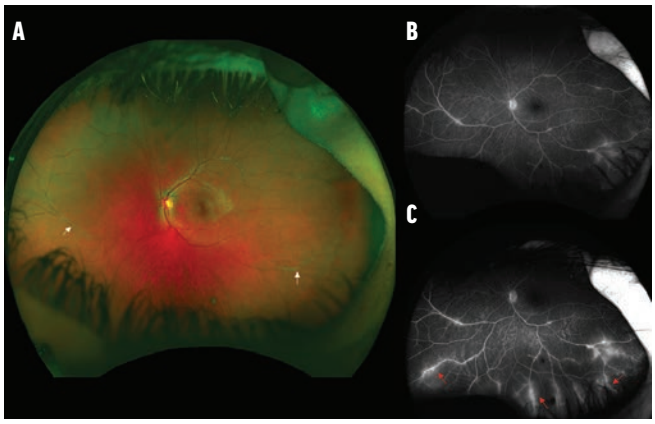



Figure 1. This fundus photograph shows perivascular sheathing (A, white arrows). Widefield intravenous FA with an on-axis view shows a perivascular leak in the posterior pole and the nasal and temporal periphery (B). Inferior-steered widefield FA shows additional areas of perivascular leakage not seen on the on-axis image (C).

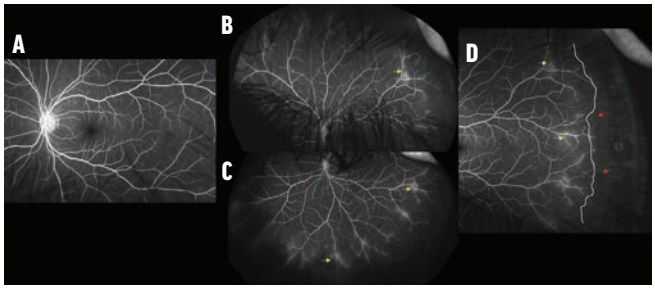



Figure 2. FA shows an unremarkable posterior pole with no optic disc leakage or angiographic macular edema (A). The peripheral-steered images show a perivascular leak superiorly (B, yellow arrows), inferiorly (C), and temporally (D). The white line temporally demarcates an area of retinal nonperfusion.

retinal periphery using steered images to accurately detect and monitor peripheral leakage (Figures 2 and 3) until complete quiescence is demonstrated on both FA and clinical examination.

Another useful marker to detect inflammatory activity is noncystic thickening (thickening of retina in absence of intraretinal fluid or intraretinal cysts) seen on thickness maps and the central subfield thickness value on OCT (Figure 4). When assessing noncystic thickening, clinicians must ensure that the segmentation lines on the OCT image are correct; otherwise, it may lead to erroneous measurements and thickness maps.

In children with intermediate uveitis and retinal vasculitis, it is also important to evaluate for retinoschisis, particularly in the inferior periphery in areas of snowbanks, as poor inflammatory control may lead to the progression of retinoschisis and retinal detachment. A vitreous hemorrhage may also develop due to traction and neovascularization because of peripheral nonperfusion. OCT and OCTA are helpful to evaluate for inflammatory choroidal (or macular) neovascular membranes that, if active, may require treatment.

Failure to fully control retinal vasculitis leads to recalcitrant cases that cannot taper IMT, which causes long-term complications and a poor prognosis. It is critical to objectively assess

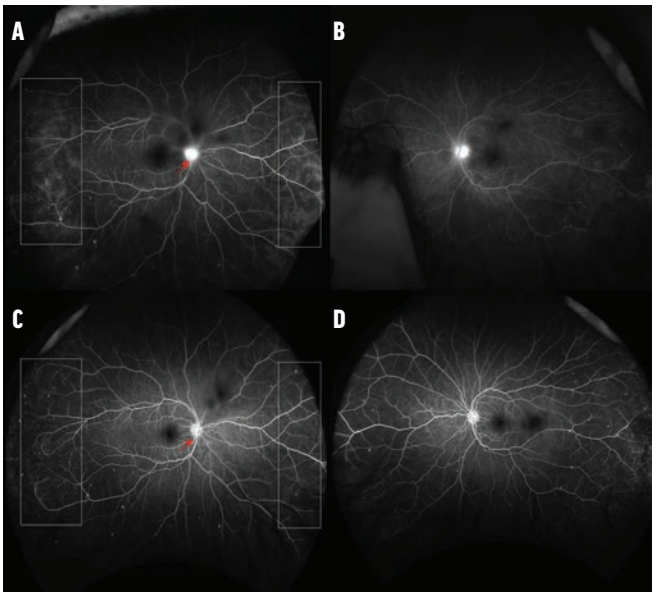



Figure 3. The widefield FA of an 8-year-old boy with active intermediate uveitis shows leakage at the optic disc (red arrow) and perivascular leakage in the periphery (white rectangles) in both the right (A) and left (B) eyes. After initiation and titration of IMT, there is improvement with resolution of the optic disc leakage (red arrow) and peripheral perivascular leakage (white rectangles) in both the right (C) and left (D) eyes.

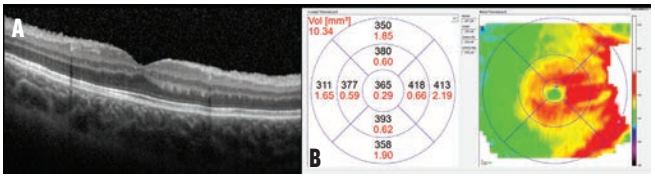



Figure 4. Although OCT shows no cystoid macular edema (A), the thickness map shows increased thickness in the corresponding scale on the right (B), consistent with noncystic thickening, which is a marker of active inflammation.

inflammation to titrate IMT and avoid premature cessation of therapy. In children, clinicians can't rely on symptoms or the anterior segment examination alone.

## THE TREATMENT

Treatment of pediatric uveitis and retinal vasculitis is individualized based on the patient and the severity of intraocular inflammation using a stepladder approach. It is important to consider the side effect profile of each treatment option. For example, systemic steroids are a good first-line treatment as a bridge to IMT. However, long-term use of steroids is not recommended due to the systemic side effects such as growth retardation, Cushingoid effects, behavioral changes, and related psychosocial problems.

Our systemic immunosuppressive therapy armamentarium includes antimetabolites (azathioprine, methotrexate, and mycophenolate mofetil [CellCept, Genentech/Roche]); calcineurin inhibitors (cyclosporine and tacrolimus), and biologics (adalimumab [Humira, AbbVie],

*(Continued on page 20)*

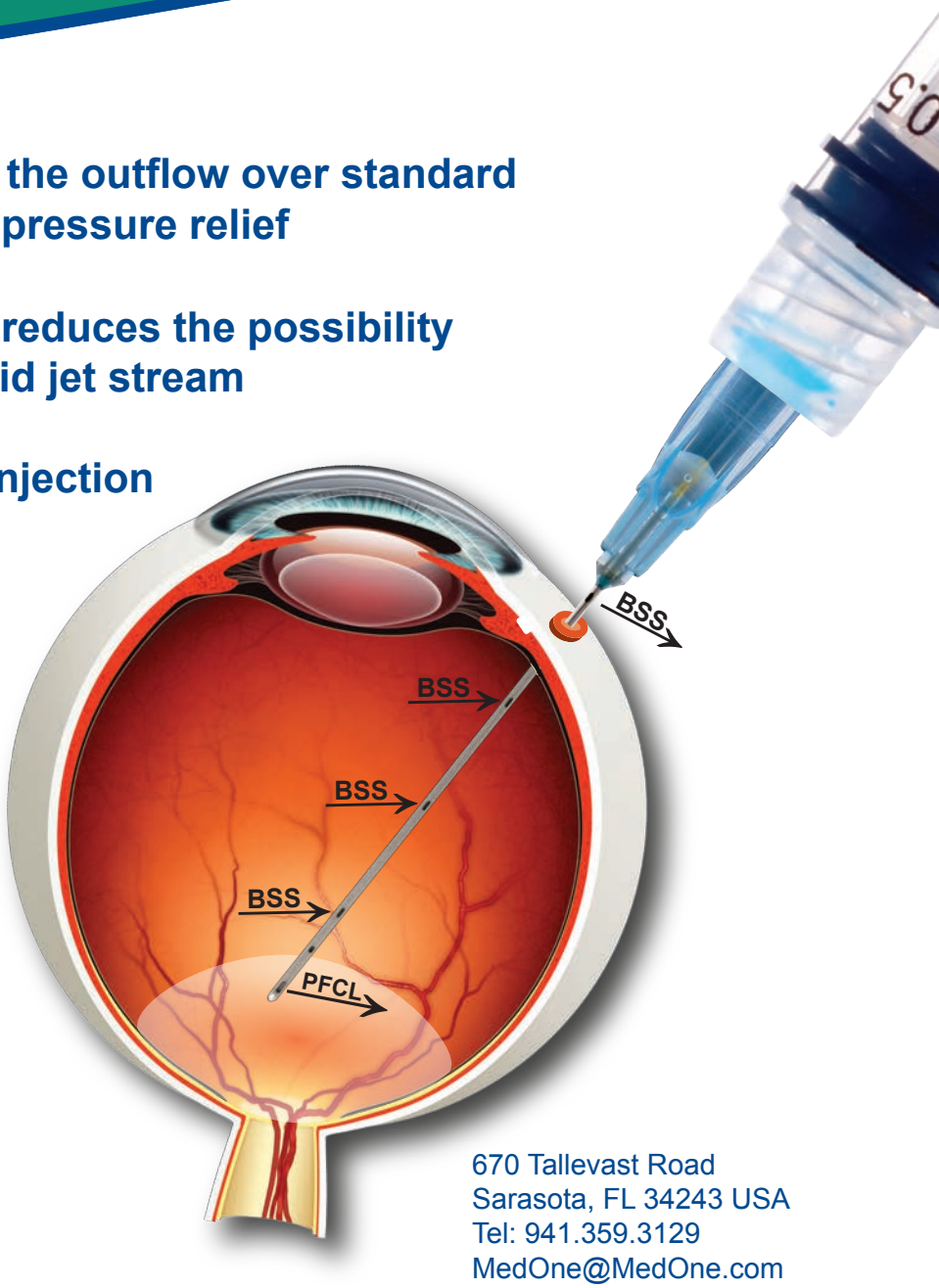
# Works Best Under Pressure!

## *DualBore SideFlō® Cannulas*

**Optimized for simultaneous relief of pressure during injection of surgical liquids such as perfluorocarbon or staining dye in small gauge surgery.**

- **Multiple egress vents double the outflow over standard DualBore cannulas for faster pressure relief**
- **Innovative side-port delivery reduces the possibility of retinal injury caused by fluid jet stream**
- **Maintains stable IOP during injection**
- **Available in 23g, 25g & 27g**

Patent #9937300




MedOne®

www.medone.com

670 Tallevast Road
Sarasota, FL 34243 USA
Tel: 941.359.3129
MedOne@MedOne.com

# IT TAKES A VILLAGE TO MAKE A DIAGNOSIS


Collaboration is crucial when you're stumped with a tough case.

BY CASSIE LUDWIG, MD, AND NIMESH A. PATEL, MD

## CASE PRESENTATION

A 52-year-old healthy male was referred to us for a macular hemorrhage in the left eye that was found on a routine optometric eye examination. His VA was 20/20 OU. His medical history was significant for creatine supplementation coupled with fasting without water for religious reasons. He had grown up in Somalia and moved to the United States at a young age. Based on fundus imaging of the left eye, he was initially presumed to have a small branch vein occlusion (Figure 1).

At the 1-month follow-up, however, his VA dropped to 20/150 OS and significant temporal retinal atrophy was noted on fundus examination and OCT (Figure 2). Fluorescein angiography showed late perifoveal leakage that did not fit a clear vascular pattern (Figure 3). At this time, given the retinitis and vision loss, there was concern for an alternative etiology.

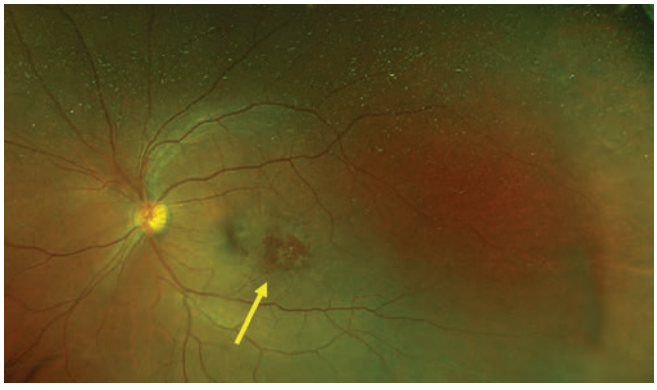


Figure 1. Fundus photography at his initial retina visit raised concern for a small branch vein occlusion (yellow arrow).

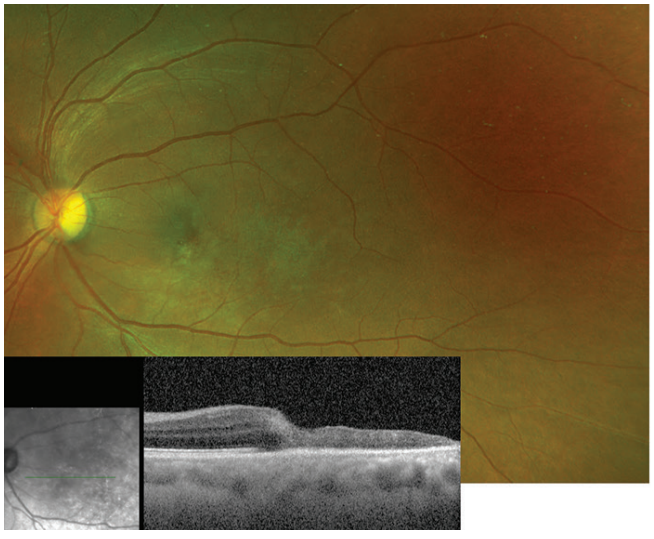


Figure 2. The fundus photograph and OCT at the 1-month follow-up showed significant temporal retinal atrophy.

## A DIAGNOSTIC ODYSSEY

An extensive diagnostic evaluation was undertaken. The first set of tests showed mild anemia and slight vitamin B12 deficiency. Infectious labs for syphilis (rapid plasma reagin and fluorescent treponemal antibody absorption), tuberculosis (QuantiFERON-TB Gold), and human immunodeficiency virus were negative.

The inflammatory workup—sarcoidosis (angiotensin converting enzyme, lysozyme, chest x-ray, and CT scan), lupus (antinuclear antibody [ANA]), and antineutrophilic cytoplasmic antibody associated vasculitis—was also negative. Hypercoagulable tests for protein C and S deficiency were negative, and Factor V Leiden thrombophilia, homocystinuria, antiphospholipid syndrome (anticardiolipin antibodies and anti-beta-2 glycoprotein), and plasma cell dyscrasias (serum protein electrophoresis) were unrevealing.

### Second Opinions

Given the atypical presentation in an otherwise healthy male, additional opinions were gathered from medical retina diagnosticians. The first recommended adding Lyme disease testing, and the second endorsed checking for toxoplasmosis. A third expert considered the possibilities of anemic retinopathy, Chikungunya virus, and West Nile virus. Each of these tests returned negative, however, and the patient had normal cardiac and carotid ultrasonography.

Figure 3. Late perifoveal leakage on fluorescein angiography did not reveal a clear vascular pattern.

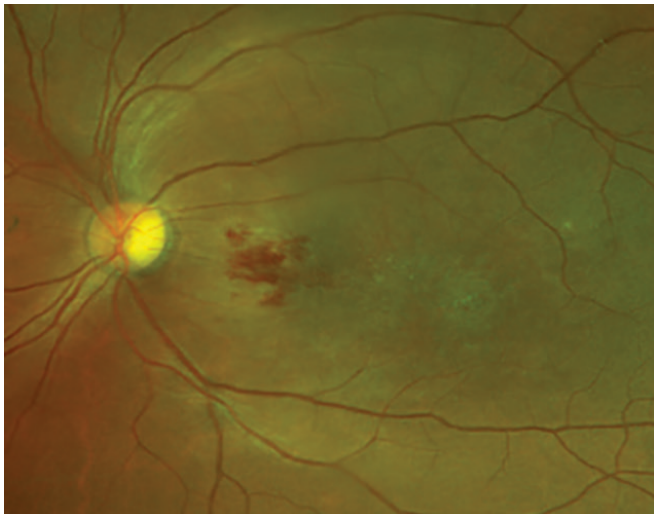


Figure 4. New nasal perifoveal intraretinal hemorrhage and focal retinitis noted on his retina follow-up visit.

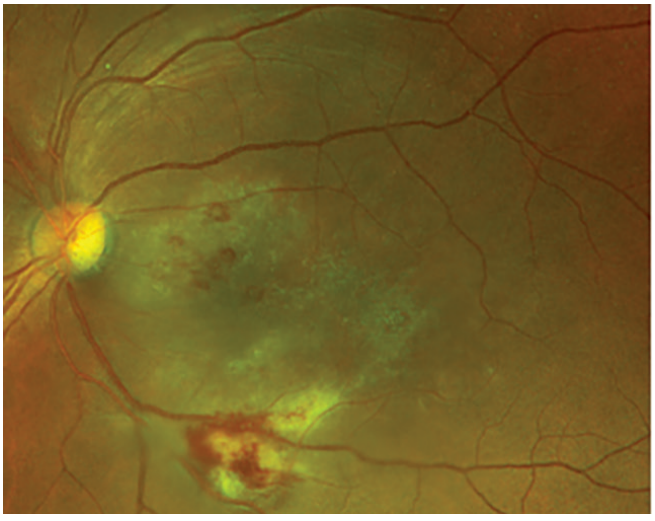


Figure 5. The patient presented for another follow-up visit, this time with a new focality of intraretinal hemorrhage with retinitis along the inferior arcade.

At his next follow-up 1 month later, the patient presented with an alarming new area of nasal perifoveal intraretinal hemorrhage and focal retinitis (Figure 4). A uveitis expert was consulted at this time, who recommended testing for Behçet syndrome (HLA-B51) and bartonella (IgG/IgM) and testing again for erythrocyte sedimentation rate, c-reactive protein, and ANA. Each of these tests returned normal. The consultant recommended trialing 60 mg prednisone daily with taper, given the negative infectious workup thus far.

The patient presented again after 1 month with another focality of intraretinal hemorrhage with retinitis along the inferior arcade (Figure 5). The prednisone was then discontinued. The next retinal consultant suggested the possibility of malaria, and another considered diffuse unilateral subacute neuroretinitis. However, a peripheral blood smear was negative, and no nematode was found.

## AN ANSWER AT LAST

Finally, it was suggested that, given the unilateral and localized nature, the condition still might be infectious and that an anterior chamber paracentesis should be performed, despite a lack of intraocular inflammation. The aqueous returned positive for cytomegalovirus (CMV) IgG and IgM. Additional serologies were sent, which confirmed CMV viremia.

The patient was given intravitreal ganciclovir, started on oral valganciclovir, and closely monitored by an infectious disease specialist. He required four doses of intravitreal ganciclovir before the retinitis resolved.

At the 1-year follow-up, the patient remains stable with no involvement of the right eye. As an atypical case of immunocompetent CMV viremia, the patient is being monitored closely by retina, infectious disease, and hematology/oncology teams.

## LEARNING POINTS

From a medical standpoint, this case illustrates that CMV retinitis can present in relatively immunocompetent patients. Although there were some minor systemic abnormalities, the patient was far from the typical compromised

AS CLINICIANS, WE ARE UNLIKELY TO SEE ALL THE VARIOUS PRESENTATIONS OF CONDITIONS IN RESIDENCY AND FELLOWSHIP.

patient (ie, those with CD4 count < 50 or those who are undergoing chemotherapy).

This experience demonstrates that it can take a village of experts to solve a challenging case. As clinicians, we are unlikely to see all the various presentations of conditions in residency and fellowship. Some cases can stump even leading experts, and medical retina can be just as, if not more, trying than surgical retina. For this reason, it is imperative that junior attendings ask for advice when needed. When working on this case, it was uplifting to receive immediate and detailed responses from busy leading authorities, some of whom we had not interacted with before.

The primary avenue of communication was the traditional method of email; however, we also used alternative means, including WhatsApp and telegram messaging services with large retina groups, who offered advice in real time.

## TAKEAWAYS

Although this case presented difficulties, it was ultimately a positive outcome in that the correct treatment was initiated prior to systemic infection, which may have affected the contralateral eye or other organs. We are fortunate to have a collaborative field, and we should take advantage of our networks to provide optimal care and accurate diagnoses, especially for atypical cases like this one. ■

**CASSIE LUDWIG, MD**
- Vitreoretinal Surgeon, Stanford University School of Medicine, Stanford, California
- Co-Founder, Healyx Labs, Stanford, California
- Financial disclosure: None

**NIMESH A. PATEL, MD**
- Vitreoretinal Surgeon, Massachusetts Eye and Ear, Boston
- Assistant Professor of Ophthalmology, Harvard Medical School, Boston
- Director of Pediatric Retina, Boston Children's Hospital, Boston
- nimesh_patel2@meei.harvard.edu
- Financial disclosure: None





*(Continued from page 16)*

infliximab [Remicade, Janssen], rituximab [Rituxan, Roche], and tocilizumab [Actemra, Genentech/Roche]). Alkylating agents such as cyclophosphamide and chlorambucil are rarely used in the pediatric population.

Local therapies such as intravitreal or periocular steroids are not usually a good option in the pediatric population. This is due to the risk of IOP elevation and cataract formation and the need to administer these injections under general anesthesia. However, in certain situations—and when used judiciously—local therapy can be an effective tool and a useful adjunct to IMT.[11,12] Dexamethasone can cause less IOP elevation compared with triamcinolone and fluocinolone. The effect of the dexamethasone implant has been shown to last for more than 6 months.

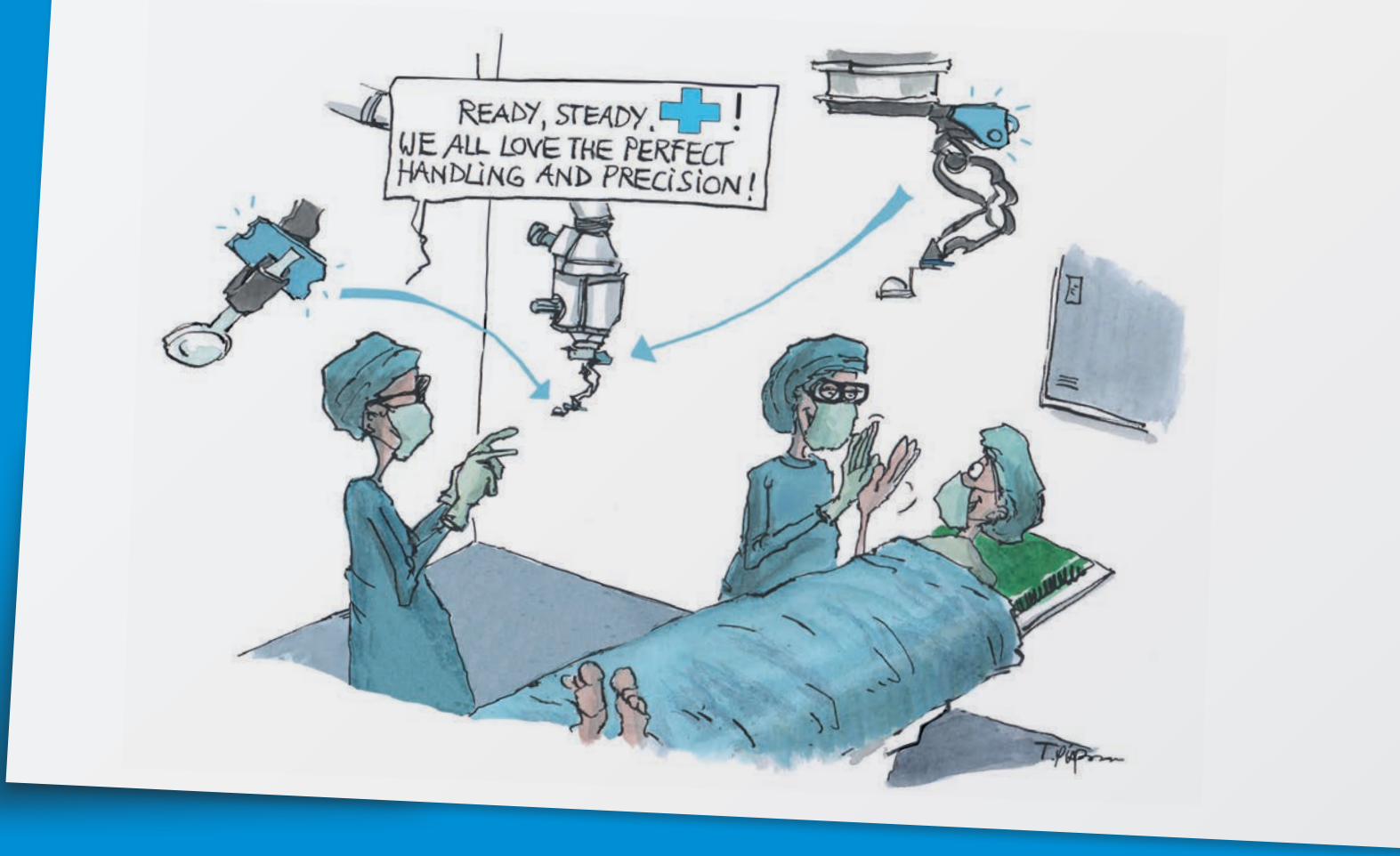
There is a higher risk of steroid-induced glaucoma in children, so it is important to involve our glaucoma colleagues early in the management plan in the event incisional glaucoma surgery is required. In addition, due to the need for chronic treatment and the risk of amblyopia, children should be followed regularly for the development of lens opacities.

The goal of IMT in pediatric uveitis is steroid-free remission without any active or recurrent inflammation (on both clinical examination and FA) on a stable IMT dose for 2 to 3 consecutive years. Once this is achieved, specialists can attempt to slowly taper the IMT off with the final goal of durable drug-free remission.[13] It is important to accurately detect the level of inflammatory activity in such children using FA during the taper.

Aggressive and adequate treatment of ocular inflammation is critical to optimize long-term visual outcomes in children with retinal vasculitis. ■

1. Thorne JE, Suhler E, Skup M, et al. Prevalence of noninfectious uveitis in the United States: a claims-based analysis. *JAMA Ophthalmol*. 2016;134(11):1237-1245.
2. Sauberan DP. Pediatric uveitis. *Int Ophthalmol Clin*. 2010;50(4):73-85.
3. Tugal-Tutkun I. Pediatric uveitis. *J Ophthalmic Vis Res*. 2011;6(4):259-269.
4. Calvo CM, Hartnett ME. The utility of ultra-widefield fluorescein angiography in pediatric retinal diseases. *Int J Retina Vitreous*. 2018;4:21.
5. Kothari N, Pineles S, Sarraf D, et al. Clinic-based ultra-widefield retinal imaging in a pediatric population. *Int J Retina Vitreous*. 2019;5(Suppl 1):21.
6. Temkar S, Azad SV, Chawla R, et al. Ultra-widefield fundus fluorescein angiography in pediatric retinal vascular diseases. *Indian J Ophthalmol*. 2019;67(6):788-794.
7. Karel I, Peleska M, Divisová G. Fluorescence angiography in retinal vasculitis in children's uveitis. *Ophthalmologica*. 1973;166(4):251-264.
8. Abraham A, Saboo US, Ducca BL, Lawand AT, Ronconi C, Cao JH. The detection of occult retinal vasculitis on fluorescein angiography in pediatric uveitis. *Ophthalmol Retina*. 2020;4(2):198-203.
9. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol*. 2005;140(3):509-516.
10. Yang P, Zhong Z, Su G, et al. Retinal vasculitis, a common manifestation of idiopathic pediatric uveitis? *Retina*. 2021;41(3):610-619.
11. Sella R, Oray M, Friling R, Umar L, Tugal-Tutkun I, Kramer M. Dexamethasone intravitreal implant (Ozurdex) for pediatric uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(10):1777-1782.
12. Tomkins-Netzer O, Talat L, Seguin-Greenstein S, Bar A, Lightman S. Outcome of treating pediatric uveitis with dexamethasone implants. *Am J Ophthalmol*. 2016;161:110-115.e111-112.
13. Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. *Surv Ophthalmol*. 2016;61(1):1-17.

**DILRAJ S. GREWAL, MD**
- Retina Surgeon and Uveitis Specialist, Duke University Eye Center, Durham, North Carolina
- dilraj.grewal@duke.edu
- Financial disclosure: Consultant (Allergan/AbbVie, EyePoint)




# BIOM® ready+

## Get ready for the extra plus in your O.R.

Experience fundus viewing at its best! As the name suggests, the new BIOM® ready+ offers quite a few plus points:

- **Adjustable lens retainer**
  To optimally centre the fundus image
- **Newly designed pivot joint**
  For even greater mechanical stability
- **Ideal for 3D Heads-up systems**
  Its optic never shows the slightest trace of use



www.oculussurgical.com +49 641 2005-298 855-SDI-BIOM (Toll Free, US Only)

OCULUS® SURGICAL

# PNEUMATIC RETINOPEXY: COMMON MYTHS DISPELLED



PnR should be considered as first-line therapy in certain cases of retinal detachment.

BY MOHAMMED AL-FALAH, MD, FRCSC; RAJEEV H. MUNI, MD, MSC, FRCSC; AND PETER J. KERTES, MD, FRCSC

Pneumatic retinopexy (PnR) can be an alternative for select cases of rhegmatogenous retinal detachment (RRD), as it avoids the potential complications of invasive procedures such as scleral buckle or pars plana vitrectomy (PPV). However, advances in PPV have made it the standard procedure for RRD in most parts of the world.[1]

Despite the popularity of PPV, there are specific cases where PnR tends to be the better technique. In this article, we address the misconceptions that cause retina specialists to shy away from PnR as first-line therapy.

## THE EVIDENCE FOR PNEUMATIC RETINOPEXY

Hilton et al reported a success rate of 84% in their series of 100 RRD cases treated primarily with PnR.[2] The first randomized controlled trial that compared PnR with scleral buckle reported a single-operation success (SOS) rate of 73% versus 82%, respectively. However, any subsequent procedure, including additional laser, cryoretinopexy, or supplemental gas injection, was considered a treatment failure in this study.[3] In 2019, the PIVOT trial showed that primary anatomic reattachment was achieved at 12 months in 80.8% of cases with PnR versus 93.2% with PPV.[4]

The PIVOT trial also demonstrated that visual acuity outcomes with PnR exceeded those with PPV by 4.9 ETDRS letters at 12 months. In addition, the composite 25-item National Eye Institute Visual Function Questionnaire scores were superior for PnR at 3 and 6 months, and vertical metamorphopsia scores were superior for the PnR group compared with the PPV group at 12 months. Of phakic patients in the PPV arm, 65% underwent cataract surgery in the study eye before 12 months versus 16% in the PnR group.[4]

Brosh et al showed that retinal displacement was evident in 44.4% of cases with PPV versus 7% with PnR.[5] The subsequent ALIGN trial demonstrated similar results and found an association between retinal displacement and postoperative anisekonia.[6]

## PNEUMATIC RETINOPEXY MYTHS DISPELLED

Below, we address 10 of the most common myths causing retina surgeons to avoid PnR as a first-line treatment for appropriate RRD cases.

### 1 Myth: PnR should be avoided, as it has a lower SOS rate than PPV.

Although it is true that vitrectomy has a marginally higher SOS, surgeons should remember that PnR can provide better functional outcomes in some cases. It is also important to consider that even though the SOS with PPV is marginally higher, the "integrity" of retinal reattachment in terms of retinal displacement, outer retinal folds, and outer retinal band discontinuity is worse with PPV.

Based on the 12% difference in SOS in the PIVOT trial (93% for PPV vs 81% for PnR), surgeons who choose PPV over PnR each time may be performing PPV unnecessarily on 8.33 patients to spare one patient from needing a second operation.[7]

Although SOS is an important outcome, functional and visual outcomes are more important to patients and should be more important to surgeons. The PIVOT trial has shown that PnR patients experienced better visual acuity outcomes by 1 line, less vertical metamorphopsia, improved vision-related quality of life, and a lower incidence of cataract in phakic patients.[4]

### 2 Myth: Patients will not adhere to the PnR postoperative positioning.

Positioning is important for the success of PnR, and there are patients who will have difficulty with this aspect. However, the same is true for PPV, and with proper coaching and encouragement, most patients are motivated and will try their best to avoid the need for more invasive surgery. Surgeons must educate patients and their companions regarding the proper sequence of postoperative positioning.

In our clinic, we provide the positioning instructions on

**ALTHOUGH SINGLE-OPERATION SUCCESS IS AN IMPORTANT OUTCOME, FUNCTIONAL AND VISUAL OUTCOMES ARE MORE IMPORTANT TO PATIENTS AND SHOULD BE MORE IMPORTANT TO SURGEONS.**

a handout as a written reminder. Showing patients their widefield fundus photos before and after the procedure will allow them to see their progress and further encourage them to adhere to the postoperative instructions.

### 3 Myth: Frequent follow-up visits create a higher burden.

With PnR, the procedure can be offered in-office at the time of presentation without delay, so the patient will not need to make another visit for surgery. If a two-step PnR is done (as is our preference), patients will be seen 1 to 2 days later for laser retinopexy. Our usual protocol is to bring the patient back in 2 days to maximize the likelihood of complete resolution of subretinal fluid (SRF) under the tear and improve our ability to perform laser retinopexy without the need for an extra visit.

The next follow-up visits are usually scheduled at weeks 1, 2, 4, and 2 months. This is approximately one more visit than is often scheduled for PPV patients, and this small difference is corroborated by the PIVOT trial.[4] When surgeons are just starting with PnR, it might be wise to bring patients back more frequently, until they become more comfortable.

### 4 Myth: PnR makes subsequent PPV more challenging.

In a phakic patient with intraocular gas, vitrectomy can be more difficult due to posterior lens feathering while lying supine, which can be easily mitigated.

In the preoperative period, patients should not lie supine, but they can be upright with their head down. In addition, they should avoid lying on their backs until it is time for the block to be given or until the time of surgery. This will prevent lenticular gas touch and reduce the risk of intraoperative cataract or lens opacification. The surgeon must remove the gas at the start of the vitrectomy.

Another complication that can arise with PnR is the presence of subretinal gas. This is exceedingly rare and can almost always be avoided with proper technique. If it does occur, most subretinal gas can be massaged out of an open break with a scleral depressor with the patient lying supine. If there is a small amount of subretinal gas that is away from the break, it is usually of no consequence.

Most pneumatic cases that require surgery have already had an incomplete response to PnR, and what may have previously been a bullous fovea-off RD is generally considerably less bullous, often with the fovea attached, which makes the vitrectomy and the shaving of the vitreous base easier.

### 5 Myth: Lasering under the gas bubble is too difficult.

Surgeons should start with simple cases and more compliant patients. Careful initial examination and mapping the exact location of the retinal tear(s) in relation to the retinal blood vessels, adjacent hemorrhages, or pigment serves as a roadmap as to where surgeons should be applying laser treatment after gas injection.

Taking widefield fundus photos can also help guide surgeons. For small breaks that may be hard to find, consider applying laser around the tear with scleral depression if the RRD is not too bullous, or at the ora in the same meridian where the retinal tear is before the gas injection.[8,9]

In some cases, surgeons should place the scleral depressor directly over the sclera when performing scleral depression. This can allow the surgeon to indent posteriorly enough to open the flap and confirm visualization of the retinal tear, which has flattened post-retinal reattachment. Subconjunctival anesthesia can help make the patient more comfortable during the laser treatment.

Another option is to apply cryopexy to the break(s) prior to gas injection. Although we prefer a two-step approach, cryopexy is a good option for a one-step procedure.

### 6 Myth: PPV more effectively addresses floaters with RRD.

While true, the important question is whether patients are bothered enough by floaters post PnR to justify PPV. In our experience, symptomatic floaters are rarely mentioned by patients after successful PnR, and vitrectomy is rarely needed, as supported by the PIVOT trial.[4]

### 7 Myth: The need to peform laser 1 to 2 days post-procedure can be a challenge.

PnR has its own timing requirements when it comes to follow-up visits and laser application,

but colleagues can help. If surgeons are unavailable to perform laser retinopexy within 48 hours, they should provide their colleague with widefield fundus photos or a careful drawing to indicate the location of the causative breaks and the landmarks near them. Other options include using cryotherapy prior to the gas injection or marking the meridian where the break is with laser at the ora.

### 8 Myth: Incorporating PnR will compromise surgical outcomes.

When surgeons are first incorporating PnR into practice, they may face more challenges than expected. In our profession, we must always be open to new techniques that offer better and safer results. We have an obligation to gain familiarity with all techniques to do what is best for our patients at any given time.

### 9 Myth: PnR promotes the development of proliferative vitreoretinopathy.

There is no evidence to support this. As with any recurrent or persistent RRD, surgeons must know when and how to intervene. Both the PIVOT trial and the Pneumatic Retinopexy Trial demonstrated that there was no increased risk of proliferative vitreoretinopathy in the PnR groups.[3,4] In addition, when a PnR is failing, it is important that the surgeon move to another technique in a timely fashion to optimize final outcomes.

### 10 Myth: Residual or persistent SRF is more common with PnR.

PnR is a non-drainage procedure that relies mainly on the retinal pigment epithelium to pump out most of the SRF. Delayed resorption of SRF is sometimes encountered in PnR, similar to scleral buckle, with a reported incidence ranging from 4% to 20%.[6,10] This can usually be attributed to the chronic and viscous nature of the SRF or to the reduced capacity of the RPE pump to remove SRF.

Persistent SRF can also be seen after PPV with a reported incidence of 15%.[11] Whether the SRF is foveal or extrafoveal, there was no association between persistent subfoveal SRF and visual acuity outcomes at 1 year.[11]

There are two scenarios where residual or persistent SRF may be encountered with PnR. First, with post-PnR positioning, SRF can shift, often inferiorly. This is almost always seen in the first few days after PnR, and if it is not associated with an open break, the fluid should resolve.

In the second scenario, loculated SRF blebs are seen under the fovea on OCT. Although this finding may be undesirable and the patient may experience some reduced visual acuity or distortion as a result, it is not associated with adverse long-term visual outcomes. As with scleral buckle and vitrectomy, the SRF will resolve in time, with corresponding improvements in visual acuity.

## STRENGTHEN YOUR SKILL SET

As retina surgeons, we must master all the techniques of RRD repair and offer the best procedure for each patient, which includes PnR. There is no procedure that works in every patient's case, and a failed pneumatic case should not affect the success of any additional retinal procedure that may be required.[4] ■

1. Jackson TL, Donachie PH, Sallam A, Sparrow JM, Johnston RL. United Kingdom National Ophthalmology Database study of vitreoretinal surgery: report 3, retinal detachment. *Ophthalmology*. 2014;121(3):643-648.
2. Hilton GF, Kelly NE, Salzano TC, Thornambe PE, Wells JW, Wendel RT. Pneumatic retinopexy: a collaborative report of the first 100 cases. *Ophthalmology*. 1987;94(4):307-314.
3. Tornambe PE, Hilton GF. Pneumatic retinopexy: a multicenter randomized controlled clinical trial comparing pneumatic retinopexy with scleral buckling. *Ophthalmology*. 1989;96(6):772-784.
4. Hillier RJ, Felfeli T, Berger AR, et al. The pneumatic retinopexy versus vitrectomy for the management of primary rhegmatogenous retinal detachment outcomes randomized trial (PIVOT). *Ophthalmology*. 2019;126(4):531-539.
5. Brosh K, Francisconi CL, Qian J, et al. Retinal displacement following pneumatic retinopexy vs pars plana vitrectomy for rhegmatogenous retinal detachment. *JAMA Ophthalmol*. 2020;138(6):652-659.
6. Francisconi CLM, Marafon SB, Figueiredo NA, et al. Retinal displacement after pneumatic retinopexy versus vitrectomy for rhegmatogenous retinal detachment (ALIGN). *Ophthalmology*. 2022;129(4):458-461.
7. Kertes PJ, Hillier RJ, Muni RH. Letter to the Editor regarding Chronopoulos and colleagues "Pneumatic retinopexy, a critical reappraisal." *Surv Ophthalmol*. 2021;66(6):1073-1075.
8. Muni RH, Kertes PJ. Marking of retinal breaks in detached retina with laser photocoagulation before pneumatic retinopexy: a prospective case series. *Retina*. 2009;29(3):405-408.
9. Yan P, Minaker S, Mandelcorn ED. Laser marking of the meridian of retinal breaks at the ora: a novel technique for pneumatic retinopexy. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(6):570-572.
10. Desatnik H, Alhalel A, Treister G, Moisseiev J. Management of persistent loculated subretinal fluid after pneumatic retinopexy. *Br J Ophthalmol*. 2001;85(2):189-192.
11. Mimouni M, Jaouni T, Ben-Yair M, et al. Persistent Loculated subretinal fluid after rhegmatogenous retinal detachment surgery. *Retina*. 2020;40(6):1153-1159.

**MOHAMMED AL-FALAH, MD, FRCSC**
- Vitreoretinal Surgery Fellow, Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario
- Assistant Professor, Department of Surgery, College of Medicine, King Faisal University, Ahsa, Saudi Arabia
- Alfalah.mohammed@yahoo.com
- Financial disclosure: None

**PETER J. KERTES, MD, FRCSC**
- Vitreoretinal Surgeon, The John and Liz Tory Eye Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario
- Professor of Ophthalmology, Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario
- peter.kertes@sunnybrook.ca
- Financial disclosure: Advisory Board (Bayer, Boehringer Ingelheim, Genentech/Roche, Novartis); Financial Support to Institution (Allergan/AbbVie, Bayer, Genentech/Roche, Novartis); Financial Support (Bayer, Novartis); Equity Owner (ArcticDx)

**RAJEEV H. MUNI, MD, MSC, FRCSC**
- Vitreoretinal Surgeon, St. Michael's Hospital/Unity Health Toronto, Toronto, Ontario
- Vice-Chair of Clinical Research, Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario
- rajeev.muni@gmail.com
- Financial disclosure: Consultant (Alcon, Allergan/AbbVie, Bausch + Lomb, Bayer, Genentech/Roch, Novartis); Research Funding/Grants (Bayer, Novartis, Genentech/Roche)

# Long-term Visual Outcomes of ForeseeHome Remote Telemonitoring Program

Ten-year data from the ALOFT Study emphasize the value of this program for earlier detection of nAMD.

BY MICHAEL J. ELMAN, MD

Despite remarkable advances in the treatment of neovascular AMD (nAMD), we still face the challenge of detecting conversions from dry to nAMD earlier. Only about one-third (34%) of patients who convert to nAMD have VA of 20/40 or better at conversion; the average is usually about 20/83.[1] Our goal is not only to treat these patients but to identify them when they still have the potential to retain good vision with our current therapies. The ForeseeHome AMD Monitoring Program (Notal Vision Monitoring Center) was designed to help us do that.

## ABOUT FORESEEHOME

The ForeseeHome AMD Monitoring Program consists of three key elements.

1. First is the patient who uses the monitoring device at home to perform a basic preferential hyperacuity perimetry (PHP) test, which is analyzed by the program's proprietary artificial-intelligence algorithm and sent to the Notal Vision Monitoring Center.

2. Second is the clinician who receives feedback from the program through a secure online portal and is alerted when a significant change from baseline is detected and warrants further evaluation. At each follow-up visit, I make a point of reviewing with patients how they're doing with the system, offering consistent feedback and encouragement. When patients see that this is important to me, they understand that it's important to them.

3. The third element is the Notal Vision Monitoring Center, which enrolls patients into the program and provides comprehensive patient education, training, and compliance management.

In the AREDS2-HOME study,[2] this system worked very well, and in my practice it works well, but how does it work in many practices in the real world over time? Answering that question was the purpose of the ALOFT study.[3]

## LONG-TERM RESULTS

The ALOFT study enrolled 2,123 patients (3,334 eyes) with average baseline VA of 20/30 (Figure 1). Outcomes from the study were compared with real-world data from the IRIS® Registry of the AAO.[3]

On average upon conversion to nAMD, VA was 20/39 before therapy was initiated. At the most recent visit, the ForeseeHome patients had achieved and maintained 20/32 VA (Figure 2). This was in contrast to patients in the IRIS Registry who had converted to nAMD and whose last available VA reading was 20/83.

As for compliance, patients tested an average of 5.2 times per week over 10 years. I believe this excellent compliance speaks to the patients' understanding that this is an important safety net for them. This is underscored by consistent feedback and encouragement from physicians and staff, as well as engagement and support from the Notal Vision Monitoring Center. My practice has found referring patients to the service an easy and seamless process, where the monitoring center takes over all of the details after a simple prescription.

## PROVEN VALUE OF EARLIER DETECTION

The ALOFT study showed us that the ForeseeHome AMD Monitoring Program can make an appreciable difference in our patients' outcomes. We have the ability to potentially improve vision by starting treatment earlier and by maintaining treatment longer, regardless of the underlying reason. This program provides a model for remote monitoring in the future for medicine and particularly for ophthalmology. ■

1. Ho AC, Kleinman DM, Lum FC, et al. Baseline visual acuity at wet AMD diagnosis predicts long-term vision outcomes: an analysis of the IRIS registry. *Ophthalmic Surg Lasers Imaging Retina.* 2020;51(11):633-639.
2. AREDS2-HOME Study Research Group, Chew EY, Clemons TE, et al. Randomized trial of a home monitoring system for early detection of choroidal neovascularization home monitoring of the Eye (HOME) study. *Ophthalmology.* 2014;121(2):535-544.
3. Mathai M, Reddy S, Elman MJ, et al. Analysis of the long-term visual outcomes of ForeseeHome Remote Telemonitoring: the ALOFT study. *Ophthalmol Retina.* 2022;6(10):922-929.

**MICHAEL J. ELMAN, MD**
- Elman Retina Group, Baltimore
- elman@elmanretina.com
- Financial disclosure: Consultant, Equity Owner (Notal Vision)


Figure 1. Patient enrollment in the ALOFT study.

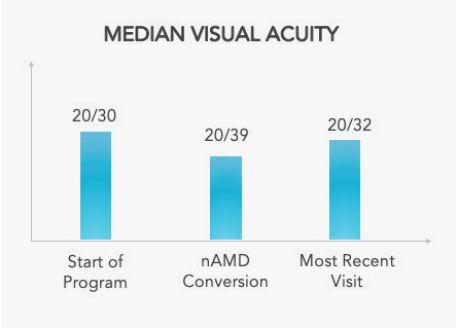



Figure 2. Median visual acuity of ForeseeHome patients.

Watch **Dr. Elman's interview** on Eyetube.net.

# TACKLE SECONDARY IOLS WITH EASE

## Experts share their tips and tricks to help you succeed with even the most challenging dislocated lens.

A CONVERSATION WITH CHRISTINA Y. WENG, MD, MBA; ASHKAN M. ABBEY, MD; MARÍA H. BERROCAL, MD; AND OMESH P. GUPTA, MD, MBA




*For secondary IOL cases, surgeons must have a host of tools and techniques at the ready. Patient education, lens choice, surgical technique, and minimizing complications are all important considerations. Here, a panel of experts discuss their techniques and tips for patients with a dislocated IOL.*

**– Rebecca Hepp, Editor-in-Chief**

### *RETINA TODAY* (*RT*): HOW DO YOU APPROACH PATIENTS WHO REQUIRE A SECONDARY IOL PROCEDURE?

**Omesh P. Gupta, MD, MBA:** The first thing I look at is the lens status and whether the patient is aphakic or pseudophakic. This seems to be a simple determination but, believe it or not, sometimes the history and medical records are not sufficient. I also look to see if there's some dislocation of the lens, any retained lens material, or vitreous prolapse.

I also consider if they have a history of glaucoma surgery, such as a tube shunt or a trabeculectomy, or if there's angle pathology or corneal endothelial disease. If they have a history of trauma or have iris defects, that may preclude an anterior chamber lens. For polypropylene or polytetrafluoroethylene (PTFE; Gore-Tex, W.L. Gore) scleral fixation, I assess the status of the conjunctiva for any scarring, a history of scleral buckling, or conjunctival retraction.

### WANT TO HEAR THE CONVERSATION AS A PODCAST?

Scan the QR code or visit New Retina Radio at eyetube.net/podcasts.

### *RT*: WHAT INFLUENCES YOUR DECISION TO RESCUE VERSUS REPLACE AN IOL?

**María H. Berrocal, MD:** I usually look at the type of lens that was dislocated. I still get PMMA IOLs, and their removal requires a very large incision, so I try to reposition those, which requires suturing them to the iris.

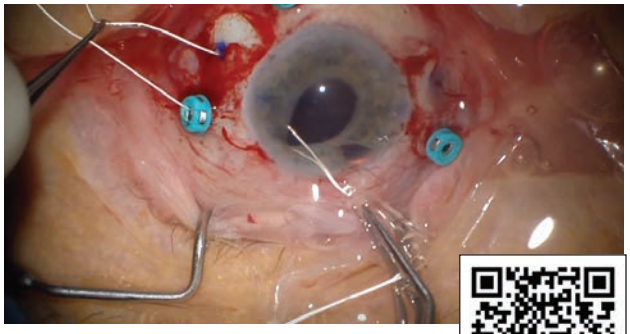
If it is a one-piece acrylic lens, I usually remove it unless the dislocation is with the entire capsule, in which case you can try to fixate the capsule with the IOL. But that is a difficult technique, so I usually replace it with a scleral-fixated three-piece IOL. I do not use anterior chamber IOLs frequently because I'm concerned many patients have low endothelial cell counts and angle or cornea problems.

**Ashkan M. Abbey, MD:** Many surgeons want to try to rescue every three-piece IOL, but in my experience, many of these IOLs will fail if you do a scleral fixation because they

### AT A GLANCE

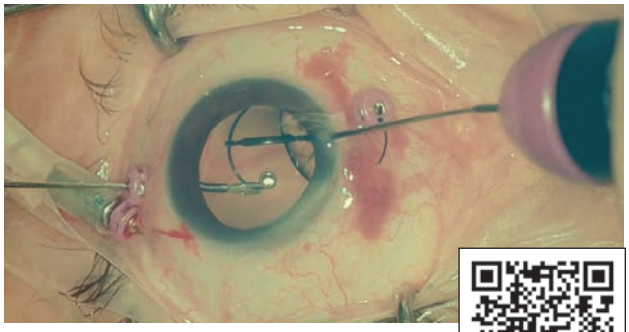
- Surgeons don't do enough secondary IOLs to master every technique; pick one and try to get as good as possible with that technique.
- Assess conjunctival mobility preoperatively and place the tunnels in the most mobile conjunctiva; avoid areas of scarring to reduce the risk of erosion.
- To combat hypotony, make the sclerotomies as small as possible and minimize instrument manipulation.

WATCH IT NOW



Video 1. Gore-Tex Fixation of a Secondary IOL

WATCH IT NOW



Video 2. IN 3D: Modified Yamane Technique for a Dislocated Three-Piece IOL

require significant manipulation to remove the residual cortex and capsule.

The best choice for those cases is to remove the lens and start over with a new three-piece IOL. I have found that the highest dislocation rates in scleral-fixated three-piece IOLs occur when you try to be a little too heroic and reposition the ones you should have removed.

**Christina Y. Weng, MD, MBA:** In addition, it is important to remind patients that this is not a simple run-of-the-mill cataract surgery. We must stress that although we aim to hit a refractive target, that may not always be possible because of the oft-complicated calculations; they should also know that recovery can take longer than what they might anticipate. Setting these expectations goes a long way toward making sure that they're happy down the line.

## *RT*: DO YOU HAVE A PREFERRED SECONDARY IOL TECHNIQUE?

**Dr. Gupta:** I most commonly scleral fixate the lens with Gore-Tex sutures (Video 1). I usually will explant the existing IOL. Surgeons don't like a lot of intraocular gymnastics to clean off a capsular bag and Soemmering ring to expose the haptics. I make sure that the intraoperative time is relatively short because that's one of the biggest issues that can increase the risk of postoperative corneal edema and cystoid macular edema.

Ultimately, it comes down to whatever technique you are comfortable with. For me, I like Gore-Tex fixation with the enVista MX60E (Bausch + Lomb). I always operate superiorly and thankfully rarely have to make adjustments for tube shunts and trabeculectomies. I don't have to worry about landmarks such as pannus because I scleral fixate at the 3:00 and 9:00 clock positions. The surgical time and refractive outcomes are predictable, and it's also an easy technique to teach to fellows. They don't have many issues with IOL tilt or centration, even with the first or second case.

**Dr. Berrocal:** Not all the lenses we want are available all the time, so my go-to technique is the modified Yamane with 27-gauge cannulas and a CT Lucia three-piece IOL (Carl Zeiss Meditec). Unlike other prolene haptics, the Lucia polyvinylidene fluoride haptics are more rigid and the chances of breaking or bending them—which can lead to decentration and astigmatism—are reduced. Also, I place the cannulas at the correct angle to perform the vitrectomy and then pull one out and reposition it (Video 2). Since it's all 27-gauge, I don't have to open a second pack, which is a big concern for surgery centers.

**Dr. Abbey:** I do the same technique, and I like using 27-gauge trocars for my tunnels (Video 3). I usually end up using five trocars total, mainly because I don't like moving everything around and manipulating myself and my hands too much during the case. I make it straightforward for every case, but I agree that the financial incentive is there to try to use just three trocars. The one thing that I like about the modified trocar-assisted scleral fixation is the efficiency. For me, that is the fastest, and I feel comfortable continuing with that one for most of my cases.

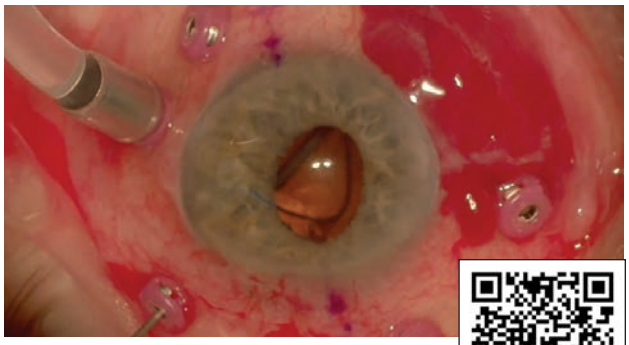
## DR. ABBEY: IS EVERYONE DOING A HANDSHAKE TECHNIQUE? NORMALLY I ALLOW THE LENS TO FALL ON THE BACK AND THEN GRAB ONE HAPTIC OFF THE RETINA TO AVOID DOING A HANDSHAKE.

**Dr. Weng:** That's a great technique, but I've gone to the handshake or hand-to-hand technique. I love working anteriorly and I find it to be fast, and you avoid having to work in a third dimension by reaching far into the vitreous cavity.

**Dr. Gupta:** I like the hand-to-hand technique for the trailing haptic side; you can pass it to yourself and then externalize it. When the IOL is sitting on the retinal surface, you can grab it nicely where you want on the leading haptic side, and that is amenable to externalizing it directly. But on the trailing haptic side, it can get a little tricky, especially when there's a nasal bridge or a deep-set orbit.

**Dr. Abbey:** I agree that the trailing haptic tends to be a problem with these cases. I always do the side that's closer to the nasal bridge first. That way, with the trailing haptic, I

WATCH IT NOW



Video 3. Transconjunctival Sutureless intrascleral (SIS) Fixation Using Trocar Cannulas

don't have to deal with the nose at all, which makes it easier to grab the haptic when it's under your viewing system. If you still can't see the haptic, push posteriorly on the optic, which usually shifts it just enough so that you can see it in the corner of your view and grab it.

**Dr. Gupta:** This technique typically fixates at the 12:00 and 6:00 clock positions, although Yamane himself does it at the 3:00 and 9:00 clock positions. I also do it at the 3:00 and 9:00 clock positions to avoid an existing or future site of a tube shunt or trabeculectomy. I want to keep that superior conjunctiva native and the sclera untouched.

**Dr. Berrocal:** For me, it's more like the 10:00 and 4:00 clock positions, or thereabouts. For people with prominent noses or deep-set eyes, I always tilt the head. I don't like taping the head so that I can tilt the head as needed to have better access during the case.

## *RT*: HOW ARE YOU PROTECTING THE HAPTICS?

**Dr. Abbey:** That starts with the preoperative planning. It's important to assess conjunctival mobility beforehand so you know where you want to put your tunnels. Place them in the most mobile conjunctiva and avoid any areas of scarring because that would increase the risk of erosion.

In addition, when I make the flange, I tuck it all the way into the tunnel until just the tip of the flange is visible under the conjunctiva. Having less surface area of the haptic helps to maintain the integrity of the conjunctiva and reduce the risk of erosion.

If and when a haptic does erode, as long as there's no infection, I often take the patient to the slit lamp, give them anesthetic drops, place a lid speculum, and trim the haptic with Vannas scissors before gently tucking it in. Usually, the conjunctiva will grow over that area.

**Dr. Berrocal:** Sometimes the haptics are too long, and if you push them in, the lens will not be centered and will be too loose. So, cutting the haptics and doing the flange is necessary. After I externalize the haptics, I play with them to make sure the IOL is perfectly centered before I trim them as needed, then flange and tuck them in.

**Dr. Weng:** Before I even burn the flanges, I make sure that I'm happy with the centration of the lens itself because sometimes by trimming one side a little bit more than the other, you can get the lens to lay in a more ideal position. The way you burn the flanges is also important. Make sure you have an even, smooth surface at the tip. That decreases the risk of conjunctival erosion.

**Dr. Abbey:** In addition to that, when you are externalizing the haptics, grab them as parallel as possible to the distal tip to prevent any kinks in the haptic itself, which can sometimes pop up underneath the conjunctiva and increase the risk of erosion.

**Dr. Gupta:** We do see erosion of Gore-Tex or conjunctival erosion in this procedure as well. To avoid this, when you are re-approximating the conjunctiva back to the limbus, drag the conjunctiva away from the site of the Gore-Tex. I drag it inferotemporally and inferonasally and anchor it to the sclera to help create a smooth, intact surface of conjunctiva over the Gore-Tex.

It's amazing how difficult it can be to take the haptic out of the tunnel in the setting of Gore-Tex fixation because Gore-Tex is porous and, over time, there's a lot of cellular ingrowth. Sometimes, it's impossible to grab the Gore-Tex on the outside of the eye or underneath the conjunctiva. I do most of my explanting from inside the eye. I cut the IOL and bring it out, grab the Gore-Tex from inside the eye, and then try to snip it and pass it through a clear corneal wound. It can be very difficult, especially if it's the external portion of the Gore-Tex that sits between the conjunctiva and sclera. That can become almost part of the eye, so I tend to leave it.

## *RT*: HOW ARE YOU MINIMIZING THE RISK OF HYPOTONY IN THE IMMEDIATE POSTOPERATIVE PERIOD?

**Dr. Weng:** Hypotony can be common in these secondary IOL cases, partly because we put so many holes in the eye and there's often a lot of manipulation. I've seen hypotony more frequently in techniques that involve inserting needles or instruments directly through the sclera, like the original Yamane technique and less commonly with the trocar-based scleral fixation.

To combat hypotony, I would recommend a few things. First, make the sclerotomies as small as possible and minimize the manipulation of the instruments through them.

Second, use an infusion line to stabilize the globe, preferably in the vitreous cavity, which is second nature to us, because often we're combining this with a vitrectomy anyway. Even if you're working only anteriorly or with your anterior segment colleagues, you can put a cannula into the anterior chamber to stabilize the globe.

Third, never hesitate to suture your wounds. I often slip my IOL in through a corneal wound, and I always throw a 10-0 nylon suture through that wound at the end of the case

to eliminate another possible point of leakage. I do the same thing with the sclerotomies, a tunnel that ends up bigger than I intended, and even around the haptic in rare cases.

If you do have postoperative hypotony, it usually has no adverse effects down the line, and many times it resolves within a week, especially with the use of postoperative topical steroids which most of us prescribe.

**Dr. Abbey:** When I reviewed my first 500 cases, I found a significant difference in hypotony rates for the sutureless scleral-fixation cases that had 27-gauge tunnels versus 25-gauge tunnels. I've gone toward using 27-gauge for the vitrectomy and for the tunnels because my data suggests that it reduces the rate of hypotony.

In addition, I've been doing a partial air-fluid exchange at the end of the case. Some people think that's going to make the lens tilt, but as long as I have flanges on my haptics, I have not seen any sort of tilt or dislocation as a result of the air-fluid exchange.

**Dr. Berrocal:** I hydrate the paracentesis and the corneoscleral wounds, which is important. Because we are using viscoelastic for these maneuvers, it helps if you don't remove it entirely; the viscoelastic can protect the eye from hypotony. With 27-gauge vitrectomy, the wounds can leak if you manipulate them, so I needle them in the opposite direction, either with a needle or with the same trocar. This helps to open up the scleral fibers and can provide closure of the sclerotomies.

**Dr. Gupta:** These are complicated eyes; they often have a history of trauma, sometimes a ruptured globe, maybe a dropped lens, and are left aphakic by the cataract surgeon. We must clean out the vitreous cavity, remove all the retained lens material, and then scleral fixate something. In addition to hypotony, ciliary body shutdown can occur, and they're not producing as much aqueous in the early postoperative period, which is an issue.

When I do scleral fixation and see a leaky wound, especially at the side of the haptic or Gore-Tex, I use a BV needle and an 8-0 vicryl suture. The needle is a nice non-spatulated needle, and you can throw the suture through the wound and stay away from your haptic or Gore-Tex. And the vicryl has a little bit of an inflammatory component, which can help to seal that wound.

## *RT*: WHAT IS YOUR TOP PEARL FOR SOMEONE WHO IS JUST STARTING TO DO SECONDARY IOLS?

**Dr. Berrocal:** Make sure to mark the incisions exactly 180° from each other. Also, if you are using trocars, angle them and put them in at the same distance so that you will not have IOL tilt.

**Dr. Abbey:** Don't be a hero. I've learned that I should not try to rescue every lens that I see. It's okay to take a lens out and start over with a fresh one; often, that gives you the best outcome visually and in terms of complication rates.

**Dr. Weng:** Marking is probably the most important step. Make sure the cornea is dry. I like using a 12-point corneal ray marker centered around the limbus.

Do a thorough job cleaning up any residual capsule that is often hiding in the sulcus. Many of these secondary IOLs sit relatively anteriorly, and occult capsular remnants can contribute to postoperative tilt.

Lastly, make sure that your trocar placement is symmetrical—not just in terms of distance posterior to the limbus, but even the angle that you're approaching your beveled tunnel and the tunnel length itself.

**Dr. Gupta:** We don't do enough of these so that we can be on autopilot. These cases always require your full attention because one step leads to another and if you mess up step one or step two, it makes it harder down the road.

We don't do enough of these to be comfortable with a variety of techniques either. My advice would be to pick one and try to get as good as possible with that technique.

These are incredibly rewarding procedures, and I would say that secondary IOLs are the number one practice builder when surgeons are coming out of fellowship. I would encourage everyone, if you haven't done so already, to give it a try. ■

**ASHKAN M. ABBEY, MD**
- Director of Clinical Research, Texas Retina Associates, Dallas
- ashkanabbey@gmail.com
- Financial disclosure: Consultant (Alcon, Alimera, Allergan/Abbvie, Eyepoint, Genentech/Roche, Outlook Therapeutics, RecensMedical, Regeneron); Equity/Stockholder (Outlook Therapeutics); Grant Support (Allergan/Abbvie, Eyepoint); Speaker (Alimera, Allergan/Abbvie, Biogen, Genentech/Roche, Regeneron)

**MARÍA H. BERROCAL, MD**
- Vitreoretinal Surgeon, CEO of Drs Berrocal & Associates, San Juan, Puerto Rico
- Editorial Advisory Board Member, *Retina Today*
- mariahberrocal@hotmail.com
- Financial disclosure: Consultant (Alcon)

**OMESH P. GUPTA, MD, MBA**
- Associate Professor of Ophthalmology, Thomas Jefferson University Hospital, Philadelphia
- Vitreoretinal Surgeon, Retina Service, Wills Eye Hospital, Philadelphia
- ogupta1@gmail.com
- Financial disclosure: Consultant (Alcon)

**CHRISTINA Y. WENG, MD, MBA**
- Professor of Ophthalmology; Fellowship Program Director, Vitreoretinal Diseases & Surgery, Baylor College of Medicine, Houston
- christina.weng@bcm.edu
- Financial disclosure: Consultant (Alcon, Alimera Sciences, Allergan/AbbVie, Dutch Ophthalmic Research Center, EyePoint, Genentech/Roche, Novartis, Opthea, Regeneron, Regenxbio)

# MACULAR HOLE SURGERY ROUNDUP

## What are the latest advances, techniques, and controversies?

BY SOPHIE J. BAKRI, MD

The concept of modern macular hole (MH) surgery was first described by Kelly and Wendel in 1991.[1] Since then, the technique has evolved considerably, and the success rates for MHs < 400 µm now approach 95% to 100%.[2]

For most vitreoretinal surgeons, the standard technique includes a pars plana vitrectomy, internal limiting membrane (ILM) peel, and gas tamponade. Surgeons should meticulously shave the vitreous base to reduce the risk of any postoperative retinal tears and allow a full gas bubble fill.

I stain the ILM with ICG or Brilliant Blue and perform a wide ILM peel to relieve tangential traction. I fill the eye with 20% $SF_6$ gas or 14% $C_3F_8$ and will choose the latter if the hole has had a longer duration, or if there are any inferior retinal tears. I recommend face-down positioning for 1 to 3 days.

### CONTROVERSIES

Recently, the utility of face-down positioning has been debated. Most retina surgeons agree that the gas bubble should come into contact with the hole, but full face-down positioning may not be necessary. A recent systematic review and meta-analysis found no difference in macular hole closure rates when studying eight randomized controlled trials (709 eyes). However, the researchers noted a visual benefit to face-down positioning, which was driven by large holes.[3]

Most surgeons perform an ILM peel for MHs, as it may increase the closure rate by ensuring that any epiretinal tissue is removed, as well as the scaffold for epiretinal membrane recurrence. Peeling also is known to reduce the rate of MH reopening after cataract surgery.

Creating an ILM flap is now an alternative to a traditional ILM peel. In this technique, surgeons perform a vitrectomy, assisted by triamcinolone, and laser any peripheral retinal tears to minimize manipulation at the end of surgery. The surgeon peels two strips of ILM and then flaps the remaining ILM over the macular hole, followed by an air-fluid exchange.

Even with these techniques, there is an up to 10% failure rate of conventional MH surgery. Large MHs greater than 500 µm, duration greater than 6 months, and a hole configuration with flat edges and no cystoid macular edema are all risk factors for failure to close. High myopia, concomitant macular disease, uveitis, and macular telangiectasia are also risk factors for non-closure.

### KEEP IT SIMPLE

When I'm referred a patient with a MH that has not closed with the first intervention, I often strategize to do a complex procedure. However, I often find that it's unnecessary. Perhaps the hyaloid is still attached at the macula, and I can use triamcinolone to lift the hyaloid or to check that the "wave" of hyaloid has been stripped to the periphery.

Sometimes, there's an inadequate ILM peel, which could be due to many reasons, including inability to complete the procedure safely if the patient was moving or breathing heavily under monitored anesthesia care. Sometimes inadequate staining may lead to inadequate visualization of the ILM, resulting in difficulty removing the ILM. You may even find a large peripheral vitreous skirt, which leads to a poor gas fill and lowers the chance of closure.

Thus, conventional surgery may still be a useful approach when reoperating on a failed MH closure, and the success rate can be up to 90% if there were obvious reasons for the failed first surgery. I usually use $C_3F_8$ in these cases, but I have colleagues who will use silicone oil.

### AT A GLANCE

- Most surgeons agree that the gas bubble should come into contact with the macular hole (MH), but full face-down positioning may not be necessary.
- Large MHs greater than 500 µm, duration greater than 6 months, and a hole configuration with flat edges and no cystoid macular edema are all risk factors for failure to close.
- For a persistent MH, strategies include creating a macular detachment or arcuate retinotomies, macular buckling, and scleral imbrication.

## WHEN COMPLEX IS NECESSARY

When faced with a persistent MH, some strategies focus on relaxing the retina. A few good approaches include creating a macular detachment or arcuate retinotomies, macular buckling, and scleral imbrication.

Surgeons can also increase gliosis with the use of growth factors, such as autologous platelet-rich plasma or human amniotic membrane, and employ techniques to plug the hole using an ILM free flap or a lens capsular flap. In addition, autologous neurosensory retinal flaps and human amniotic membrane (epiretinal or subretinal) are gaining in popularity.

The human amniotic membrane graft, first described by Stanislao Rizzo, MD, in 2019, is rich in growth factors, can integrate into tissue, and is noninflammatory.[4] Dr. Rizzo described subretinal implantation inside the hole and the use of air or gas. Other techniques have since evolved, such as the epiretinal patch that may include silicone oil tamponade.

Autologous retinal transplantation was developed by Grewal and Mahmoud, and results of a multicenter international collaborative study group showed complete closure in 89% of holes, with vision improving in 37%.[5]

Small macular holes can be treated medically, and a review of patients showed that these holes can close with topical antiinflammatories or carbonic anhydrase inhibitors in approximately 5.6 weeks.[6]

## QUESTIONS REMAIN

MH surgery has evolved considerably since the initial description in 1991. Questions surrounding MH surgery that remain include: "should we peel the ILM?" "Which gas should we use, or should we use oil?" "How long should the patient position face-down, or is it even necessary?"

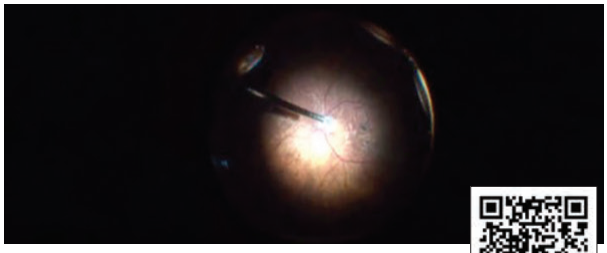
Nonetheless, there are evolving techniques for the management of refractory and large MHs that were previously considered inoperable. ■

1. Kelly NE, Wendel RT. Vitreous surgery for idiopathic macular holes. Results of a pilot study. *Arch Ophthalmol.* 1991;109(5):654-659.
2. Ittarat M, Somkijrungroj T, Chansangpetch S, Pongsachareonnont P. Literature review of surgical treatment in idiopathic full-thickness macular hole. *Clin Ophthalmol.* 2020;14:2171-2183.
3. Chaudhary V, Sarohia GS, Phillips MR, et al. Role of positioning after full-thickness macular hole surgery: a systematic review and meta-analysis [published online ahead of print July 1, 2022]. *Ophthalmol Retina.*
4. Rizzo S, Caporossi T, Tartaro R, et al. A Human amniotic membrane plug to promote retinal breaks repair and recurrent macular hole closure. *Retina.* 2019;39(Suppl 1):S95-S103.
5. Grewal DS, Mahmoud TH. Autologous neurosensory retinal free flap for closure of refractory myopic macular holes. *JAMA Ophthalmol.* 2016;134(2):229-230.
6. Niffenegger JH, Fong DS, Wong KL, Modjtahedi BS. Treatment of secondary full-thickness macular holes with topical therapy. *Ophthalmol Retina.* 20204(7):695-699.

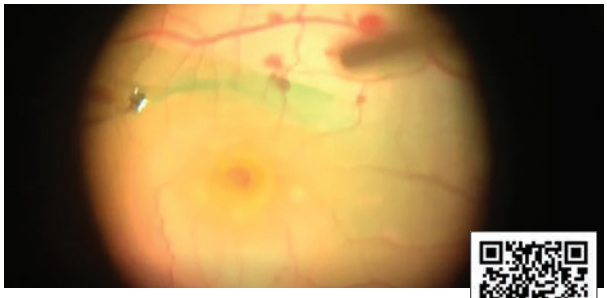
*Editor's note: This content was first presented at AAO 2022 in Chicago on October 1.*

**SOPHIE J. BAKRI, MD**
- Chair, Department of Ophthalmology; Whitney and Betty MacMillan Professor of Ophthalmology, Mayo Clinic, Rochester, Minnesota
- bakri.sophie@mayo.edu
- Financial disclosure: None

## MACULAR HOLE APPROACHES ON EYETUBE

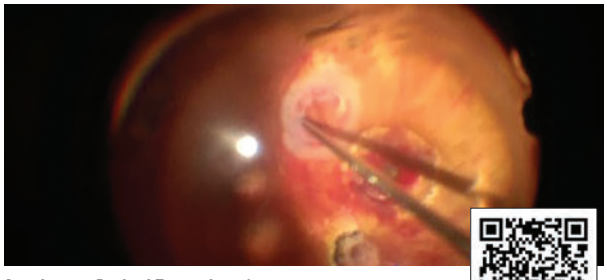


An Inverted ILM Flap for an Atrophic Macular Hole



Superior Wide-Base ILM Flap Transposition (SWIFT) Technique for Macular Hole Closure

Stuff-In Technique With Brilliant Blue Dye and Perfluorocarbon Liquid for Large Macular Holes



Autologous Retinal Transplant for a Full-Thickness Macular Hole

Plasma-Assisted Macular Hole Closure

# OPTIC DISC PIT MACULOPATHY: TODAY'S TREATMENT OPTIONS

When treatment of an associated serous retinal detachment is warranted, these pearls can guide your clinical approach.

BY DANIEL SU, MD, AND DAVID BOYER, MD


Optic disc pit is a rare, congenital excavation of the optic nerve head. Its etiology is thought to be an incomplete closure of the embryonic fissure during fetal development, similar to other congenital optic disc anomalies such as morning glory syndrome and optic nerve colobomas.[1] Optic pits are usually unilateral, although up to 15% are bilateral. Most pits are located at the inferotemporal aspect of the disc and appear as a grayish, oval-shaped depression on a fundoscopic examination (Figure).

Although patients with optic disc pits are often asymptomatic, visual field defects have been described. The defects are most commonly an enlarged blind spot or a paracentral scotoma.[1,2] However, up to half of the cases can be complicated by optic pit-associated maculopathy—retinoschisis-like changes and serous macular detachment—that can be associated with significant deterioration in vision.[3] Optic pit maculopathy occurs equally in males and females and usually appears in the third or fourth decade of life.

## CURRENT HYPOTHESES

The exact etiology of optic disc pit leading to serous retinal detachment remains unclear, although there are two leading hypotheses. The first postulates that vitreous traction on the optic disc pit and macula results in a negative pressure gradient, allowing vitreous fluid to enter through the pit and into the submacular space.[1,4] In one series, vitreous traction was observed with OCT in the majority of patients with optic disc pit maculopathy.[5] The second hypothesis suggests that the optic pit defect creates a direct communication between the subarachnoid and subretinal spaces, allowing cerebral spinal fluid (CSF) to create the serous retinal detachment.[6] In support of this hypothesis, Kuhn et al presented a case report of a patient with optic disc pit associated serous detachment who underwent pars plana vitrectomy (PPV) with silicone oil.[7] During an evaluation for persistent headaches years later, emulsified silicone oil was seen intracranially on MRI of the head. The emulsified oil presumably passed from the vitreous cavity through the optic disc pit into the CSF space then intracranially.

Although spontaneous resolution with improvement in symptoms has been reported, untreated optic disc pit maculopathy typically leads to progressive vision loss with overall poor outcomes.[8-10] Therefore, specialists should offer treatment with minimal delay.

## POTENTIAL TREATMENTS

Because optic disc pit maculopathy is rare, there is no clear consensus on the most effective treatment. A wide variety of treatment strategies have been described, including laser photocoagulation at the temporal disc margin, intravitreal gas injection, macular buckling, and PPV.

The rationale for laser photocoagulation at the temporal disc margin is that the chorioretinal adhesion created by the laser will serve as a barrier between the optic disc pit and

## AT A GLANCE

- Up to half of optic disc pit cases can be complicated by optic pit-associated maculopathy.
- A wide variety of treatment strategies have been described for optic disc pit maculopathy, including laser photocoagulation at the temporal disc margin, intravitreal gas injection, macular buckling, and pars plana vitrectomy.
- Most published reports of various techniques for the management of optic disc pit-associated maculopathy involve a small number of cases with limited long-term follow-up.

Figure. This fundus photograph demonstrates an optic disc pit in the inferotemporal margin of the optic nerve (arrow). There is no associated serous macular detachment in this case.

the subretinal space. In practice, the time for improvement is often long, and the laser location over the maculopapular bundle can cause significant visual field defects.[11] As a result, this treatment modality—when performed in isolation—has largely fallen out of favor.

The reasoning behind intravitreal gas injection is that pneumatic displacement may induce a posterior vitreous detachment while sealing the optic pit, resulting in macular reattachment. This technique was used in several small series with an overall 50% success rate for macular reattachment. However, more than one injection was often necessary.[12]

With macular buckling surgery, complete resorption of fluid has been reported in as high as 85% of cases. Furthermore, improvement in visual acuity has been demonstrated over long-term follow-up with low rates of recurrences.[13,14] While impressive, these results have not been replicated, and this technique has not been widely adopted.

PPV is often the treatment of choice, either alone or in combination with gas tamponade, laser photocoagulation, and internal limiting membrane (ILM) peeling. Induction of a complete posterior vitreous detachment to remove vitreous traction on the optic pit is thought to be critical for macular reattachment. Gas tamponade in combination with PPV has been suggested to help seal the optic pit and move the subretinal fluid away from the macula.[15] Endolaser on the temporal aspect of the optic nerve at the time of PPV carries the same risk of visual field defect and vision loss as when performed alone.[16] ILM peeling can help to eliminate tangential traction, and multiple reports have described good visual outcomes with PPV with ILM peeling.[17] However, some authors have reported good results without ILM peeling, and they believe it to be unnecessary.[16]

Other techniques include directly covering or plugging the optic disc pit with an ILM flap, autologous scleral flap, human amniotic membrane, or fibrin glue. A few cases using an inverted ILM flap to cover the optic disc pit in conjunction with gas tamponade have been reported with improvement in both vision and anatomy.[18-20] However, in cases where the ILM was peeled in the foveal area to create a large ILM flap, postoperative macular holes can develop with a resulting drop in vision.[21] Therefore, in cases with a thin retina over the fovea—similar to cases with high myopia—a foveal-sparing ILM peel should be considered.

Some authors advocate for plugging the pit with ILM, with the argument that covering the optic disc pit may prevent vitreous fluid from entering the subretinal space via the pit but doesn't prevent CSF from entering the subretinal space. Plugging the pit may prevent both potential sources of fluid from entering the subretinal space. One case series comparing a simple ILM flap versus plugging the optic pit with ILM demonstrated faster resolution of fluid with the plugging technique.[22]

The use of an autologous scleral tissue flap to cover or plug the optic disc pit has been reported. A few small case series showed resolution of fluid with improvement in vision.[15,23,24] One comparative case series showed similar outcomes between eyes that had an ILM flap versus those that had an autologous scleral tissue flap.[24] Autologous fibrin prepared from the patient's whole blood has also been used.[25] A report of two cases that previously did not improve with PPV and ILM peeling subsequently underwent PPV with autologous fibrin injected over the pit to seal it. Anatomic improvement was noted in both cases with the resolution of macular detachment. The use of fibrin glue over the optic pit has also been suggested.[26] More recently, human amniotic membrane has been used in a case series of 11 patients to plug the optic disc pit and demonstrated excellent visual and anatomic outcomes at 12 months.[27]

Ooto et al used PPV with inner retinal fenestration using a bent 25-gauge needle in 18 patients without laser photocoagulation to achieve anatomic and functional improvement.[28] This indicates that inner retinal fenestration can redirect fluid into the vitreous cavity instead of the retina.

## TIME TO THINK LONG-TERM

Thus far, most published reports of various techniques in the management of optic disc maculopathy involve a small number of cases with limited long-term follow-up, and potential long-term complications such as visual field loss may not yet be present. Furthermore, most studies did not perform formal visual field evaluation. The risk of direct mechanical injury to the optic nerve is likely highest with techniques where additional material is implanted directly into the optic nerve pit. These cases are challenging to manage, and there are no established guidelines for treatment.

*(Continued on page 36)*

# 10 TIPS FOR SUBRETINAL DELIVERY

Master this tried-and-true technique to help you succeed with novel therapies in the OR.

BY NINEL Z. GREGORI, MD

Subretinal delivery of therapeutic agents is a common technique employed for the displacement of submacular hemorrhage. It is now part of the surgical approach for several novel treatments, including approved and experimental gene therapy products and even a subretinal prosthesis (Prima, Pixium Vision).[1-6] Clinical trials in dry and wet AMD and inherited retinal diseases (IRDs) that cause outer retinal degeneration are exploring the subretinal delivery of viral vectors containing various genes and even clustered, regularly interspaced, short palindromic repeats (CRISPR) gene editing mechanisms to repair the genetic defect or activate pathways aimed at preserving photoreceptors and/or retinal pigment epithelial (RPE) cells.[7]

Subretinal delivery involves iatrogenic detachment of the retina inside or outside of the macula and sometimes the fovea. While the subretinal delivery technique varies slightly between trials, the common goal is to detach the retina as safely as possible, deliver the agent without causing outer retina and RPE damage, and inject enough product to see tangible improvements in patients' functional vision.[8,9]

In this article, I provide surgical pearls based on my team's broad experience delivering therapeutic agents into the subretinal space for various retinal conditions, such as retinitis pigmentosa, choroideremia, achromatopsia, Leber congenital amaurosis, dry and wet AMD, as well as administration of the FDA-approved gene therapy voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics).[9]

## 1 REMOVE THE HYALOID OVER THE INJECTION SITE

Use a staining agent (I prefer triamcinolone acetonide) to visualize the hyaloid and remove it over the treatment zone. If the posterior hyaloid looks like an adherent sheath, gently scrape it off with a membrane scraper (eg, Finesse Flex loop, Alcon) or aspirate with a soft tip to lift it from the retina before using the vitrector. If you do not lift the hyaloid, it will hinder fluid penetration through the retina when raising a bleb.

## 2 SELECT YOUR INJECTION SITE PREOPERATIVELY

Based on the study protocol, decide on your preferred injection site(s) along an easily recognizable vascular landmark. This will help locate the self-sealing penetration site if there are multiple injections administered into the same retinotomy. Typically, macular blebs are initiated along the superior temporal or inferior temporal arcade. Injecting at least 3 mm from the fovea is advisable because closer than 2 mm increases the risk of an intraoperative macular hole due to greater foveal stretch.[10] Extramacular blebs for several ongoing AMD trials are positioned inferiorly; thus, select a site away from the optic nerve to allow for bleb expansion.

## 3 ALLOW THE INJECTION FLUID TO PENETRATE AND DETACH THE RETINA

The surgeon may assume that they must push the cannula through the retina to raise a bleb. However, the *fluid* that you are injecting penetrates the retina, not the cannula. In fact, the 38- or 41-gauge cannula is so fine that pushing it firmly against the retinal tissue will occlude the lumen and make raising the bleb more difficult. The two subretinal cannulas commonly used for subretinal delivery are the 23-gauge extendable 1270.ext DORC polytetrafluoroethylene

## AT A GLANCE

- Subretinal delivery is now part of the surgical approach for several novel treatments, including approved and experimental gene therapies and even a subretinal prosthesis.
- If you do not lift the hyaloid, it will hinder fluid penetration through the retina when raising a bleb.
- Use the lowest pressure necessary to enter the subretinal space.

Figure 1. I load the therapeutic into the microinjector syringe through the front narrow end of the loading syringe to avoid air bubbles.

cannula (Dutch Ophthalmic) that tapers to 41-gauge and 23-, 25-, and 27-gauge polypropylene PolyTip cannulas (MedOne Surgical) tapering to 38-gauge (equivalent to 41-gauge in other brands). PolyTip cannulas come in 2-mm or 5-mm lengths of the 38-gauge fiber.

Place the cannula against the retina gently to avoid blanching of the RPE. I use intraoperative OCT (iOCT) to confirm that I am not generating visible retinal and choroidal indentation; if I am, I lighten my touch by lifting my instrument slightly to open the lumen while depressing the pedal to allow the fluid jet to penetrate into the subretinal space.

Injecting a balanced salt solution (BSS) to initiate the retinal detachment with a tiny pre-bleb may be helpful when the virus volume available is small.[8,10]

## 4 USE THE LOWEST POSSIBLE INFUSION PRESSURE

I use the Viscous Fluid Control (VFC) function on the Constellation (Alcon) to perform the injection under pedal control. While the exact settings will depend on the vitrectomy machine being used, the surgeon should use the lowest pressure necessary to enter the subretinal space. I typically start at 10 mm Hg to 12 mm Hg and test the cannula outside of the eye to see a steady drip, not a stream. If I have trouble raising a bleb, I increase the pressure slowly, typically to 14 mm Hg or 16 mm Hg; I rarely go up to 18 mm Hg.

Once I see subretinal fluid forming, I continue injecting at a lower injection pressure to avoid outer retina and RPE damage. The injection pressure required to overcome the retina-RPE adhesion declines exponentially with bleb diameter; thus, it may be advisable to reduce the injection pressure once the bleb starts to expand.[11]

OCT and transmission electron microscopy show that the disruption of outer retinal layers and degeneration of outer segments in monkey eyes occur after subretinal BSS injection at 20 psi, but not at 6 psi. Moreover, migration and thickening of RPE cells were both seen at 20 psi.[12]

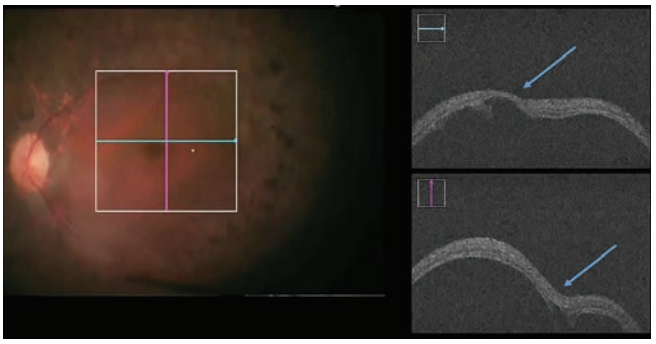


Figure 2. iOCT imaging shows a large subretinal bleb. Surgeons should monitor the fovea (blue arrows) to avoid excessive stretch or eversion.

Because the severity of retinal damage is associated with the injection pressure, the subretinal injection should be performed at the lowest pressure possible.

If the study protocol allows, I bevel the tip of the subretinal cannula at 45° to help nick the internal limiting membrane and allow the stream to penetrate the retina easily.

## 5 COVER THE TARGET TREATMENT AREA

Once the surgeon has initiated the subretinal injection, the resulting bleb may unavoidably propagate away from the target zone. If the study protocol allows, I create more than one bleb to cover the desired treatment area. Some blebs expand in an anterior/posterior rather than a horizontal direction. Surgeons can consider using a fluid-air exchange to push and spread a high bleb laterally.

## 6 AVOID INJECTING SUBRETINAL AIR

While a few tiny bubbles do not cause visible negative effects, large air bubbles add extra volume into the subretinal space, displace the gene therapy from the target tissues, and may cause a macular hole or damage the retina or RPE. To avoid this potential complication, I load the virus into a microdose injection syringe (MedOne Surgical) through the front narrow end of the loading syringe rather than aspirating directly from a vial (Figure 1).[8] I avoid aspirating air into the injection syringe and prime syringes and cannulas by pointing up to expel air bubbles.

## 7 USE INTRAOPERATIVE OCT

In addition to visualizing excessive pressure on the retina during the injection, iOCT allows me to confirm delivery into the subretinal space, monitor for inadvertent suprachoroidal injection, map the extent of fluid across the treatment zone, and monitor the fovea to avoid excessive stretching or macular hole.[13]

I use an assistant to monitor the foveal contour during subretinal injection and stop injecting if the subretinal fluid is hydrating the central macula or approaching the fovea (when foveal detachment is not desired) or if the fovea everts during subfoveal delivery (Figure 2).

## 9 ENSURE GOOD WRIST SUPPORT

Keep the cannula as steady as possible to avoid enlarging the retinotomy and to minimize reflux into the vitreous cavity. Reflux is difficult to visualize, although it likely occurs in every case to some degree.[14] iOCT may show clues, such as the bleb rising and then flattening or never rising despite presumed subretinal injection. In addition to making it difficult to calculate the actual dose delivered, reflux increases inflammation if the vector is left in the vitreous.

## 10 CLEAN UP THE VITREOUS CAVITY

Depending on the agent and the surgical protocol, at the end of the case, I either perform a fluid-air exchange or irrigate the vitreous cavity for 1 to 2 minutes with BSS and trim any peripheral vitreous that may trap viral particles.

## TAKEAWAYS

The key steps to successful subretinal delivery include: achieving posterior hyaloid detachment over the treatment zone, avoiding excessive pressure against the retina to let the fluid stream penetrate the neurosensory retina, monitoring the fovea or the treatment zone with iOCT, delivering the desired treatment volume, and removing refluxed virus from the vitreous cavity. ■


1. Haupert CL, McCuen BW 2nd, Jaffe GJ, et al. Pars plana vitrectomy, subretinal injection of tissue plasminogen activator, and fluid-gas exchange for displacement of thick submacular hemorrhage in age-related macular degeneration. *Am J Ophthalmol*. 2001;131(2):208-215.
2. Barnard AR, Groppe M, MacLaren RE. Gene therapy for choroideremia using an adeno-associated viral (AAV) vector. *Cold Spring Harb Perspect Med*. 2014;5(3):a017293.
3. Palanker DV, Le Mer Y, Hornig R, et al. Restoration of sight in geographic atrophy using a photovoltaic subretinal prosthesis. *Invest Ophthalmol Vis Sci*. 2019;60:970.
4. MacLaren RE, Bennett J, Schwartz SD. Gene therapy and stem cell transplantation in retinal disease: the new frontier. *Ophthalmology*. 2016;123(10S):S98-S106.
5. MacLaren RE, Groppe M, Barnard AR, et al. Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial. *Lancet*. 2014;383(9923):1129-1137.
6. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2017;390(10097):849-860. Erratum in: *Lancet*. 2017;390(10097):848.
7. Guimaraes TAC, Georgiou M, Bainbridge JWB, Michaelides M. Gene therapy for neovascular age-related macular degeneration: rationale, clinical trials and future directions. *Br J Ophthalmol*. 2021;105(2):151-157.
8. Davis JL, Gregori NZ, MacLaren RE, Lam BL. Surgical technique for subretinal gene therapy in humans with inherited retinal degeneration. *Retina*. 2019;39(Suppl 1):S2-S8.
9. Gregori NZ, Davis JL. Surgical observations from the first 120 cases of subretinal gene therapy for inherited retinal degenerations [preprint published online December 18, 2020]. *Retina*.
10. Xue K, Groppe M, Salvetti AP, MacLaren RE. Technique of retinal gene therapy: delivery of viral vector into the subretinal space. *Eye (Lond)*. 2017;31(9):1308-1316.
11. Kita M, Negi A, Kawano S, Honda Y, Maegawa S. Measurement of retinal adhesive force in the in vivo rabbit eye. *Invest Ophthalmol Vis Sci*. 1990;31(4):624-628.
12. Takahashi K, Morizane Y, Hisatomi T, et al. The influence of subretinal injection pressure on the microstructure of the monkey retina. *PLoS One*. 2018;13(12):e0209996.
13. Gregori NZ, Lam BL, Davis JL. Intraoperative use of microscope-integrated optical coherence tomography for subretinal gene therapy delivery. *Retina*. 2019;39(Suppl 1):S9-S12.
14. Hsu ST, Gabr H, Viehland C, et al. Volumetric measurement of subretinal blebs using microscope-integrated optical coherence tomography. *Transl Vis Sci Technol*. 2018;7(2):19.



**NINEL Z. GREGORI, MD**

- Professor of Clinical Ophthalmology, Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami
- ngregori@med.miami.edu
- Financial disclosure: Grant Support (Applied Genetic Technologies Corporation, Biogen, Gyroscope Therapeutics, Ocugen)


*(Continued from page 33)*

Currently, the predominant treatment is PPV with different adjuvant therapies. There are limited studies comparing different surgical approaches, and additional studies are needed to provide clarity on the optimal surgical approach. ■


1. Brown GC, Shields JA, Goldberg RE. Congenital pits of the optic nerve head. II. Clinical studies in humans. *Ophthalmology*. 1980;87(1):51-65.
2. Shah SD, Yee KK, Fortun JA, Albini T. Optic disc pit maculopathy: a review and update on imaging and treatment. *Int Ophthalmol Clin*. 2014;54(2):61-78.
3. Bonnet M. Serous macular detachment associated with optic nerve pits. *Graefes Arch Clin Exp Ophthalmol*. 1991;229(6):526-532.
4. Georgalas I, Ladas I, Georgopoulos G, Petrou P. Optic disc pit: a review. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(8):1113-1122.
5. Theodossiadis PG, Grigoropoulos VG, Emfietzoglou J, Theodossiadis GP. Vitreous findings in optic disc pit maculopathy based on optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol*. 2007;245(9):1311-1318.
6. Ohno-Matsui K, Hirakata A, Inoue M, et al. Evaluation of congenital optic disc pits and optic disc colobomas by swept-source optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2013;54:7769-7778.
7. Kuhn F, Kover F, Szabo I, Mester V. Intracranial migration of silicone oil from an eye with optic pit. *Graefes Arch Clin Exp Ophthalmol*. 2006;244(10):1360-1362.
8. Patton N, Aslam SA, Aylward GW. Visual improvement after long-standing central serous macular detachment associated with an optic disc pit. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(8):1083-1085.
9. Vedantham V, Ramasamy K. Spontaneous improvement of serous maculopathy associated with congenital optic disc pit: an OCT study. *Eye (Lond)*. 2005;19(5):596-599.
10. Sobol WM, Blodi CF, Folk JC, Weingeist TA. Long-term visual outcome in patients with optic nerve pit and serous retinal detachment of the macula. *Ophthalmology*. 1990;97(11):1539-1542.
11. Mustonen E, Varonen T. Congenital pit of the optic nerve head associated with serous detachment of the macula. *Acta Ophthalmol (Copenh)*. 1972;50(5):689-698.
12. Akiyama H, Shimoda Y, Fukuchi M, et al. Intravitreal gas injection without vitrectomy for macular detachment associated with an optic disk pit. *Retina*. 2014;34(2):222-227.
13. Theodossiadis GP, Theodossiadis PG. The macular buckling technique in the treatment of optic disk pit maculopathy. *Semin Ophthalmol*. 2000;15(2):108-115.
14. Theodossiadis GP, Chatzirallli IP, Theodossiadis PG. Macular buckling in optic disc pit maculopathy in association with the origin of macular elevation: 13-year mean postoperative results. *Eur J Ophthalmol*. 2015;25(3):241-248.
15. Travassos AS, Regadas I, Alfaiate M, et al. Optic pit: novel surgical management of complicated cases. *Retina*. 2013;33(8):1708-1714.
16. Avci R, Yilmaz S, Inan UU, et al. Long-term outcomes of pars plana vitrectomy without internal limiting membrane peeling for optic disc pit maculopathy. *Eye (Lond)*. 2013;27(12):1359-1367.
17. Rizzo S, Belting C, Genovesi-Ebert F, et al. Optic disc pit maculopathy: the value of small-gauge vitrectomy, peeling, laser treatment, and gas tamponade. *Eur J Ophthalmol*. 2012;22(4):620-625.
18. Mohammed OA, Pai A. Inverted autologous internal limiting membrane for management of optic disc pit with macular detachment. *Middle East Afr J Ophthalmol*. 2013;20(4):357-359.
19. Hara R, Tsukahara Y, Simoyama T, Mori S. Refined internal limiting membrane inverted flap technique for intractable macular detachment with optic disc pit. *Case Rep Ophthalmol*. 2017;8(1):208-213.
20. Sborgia G, Recchimurzo N, Sborgia L, et al. Inverted internal limiting membrane-flap technique for optic disk pit maculopathy: morphologic and functional analysis. *Retin Cases Brief Rep*. 2021;15(1):31-37.
21. Shukla D, Kalliath J, Tandon M, Vijayakumar B. Vitrectomy for optic disk pit with macular schisis and outer retinal dehiscence. *Retina*. 2012;32(7):1337-1342.
22. Ravani R, Kumar A, Karthikeya R, et al. Comparison of inverted ILM-stuffing technique and ILM peeling alone for optic disc pit-associated maculopathy: long-term results. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49(12):e226–e232.
23. Shah PK, Karandikar SS, Narendran V. Scleral autograft for optic nerve head pit associated chronic maculopathy. *Ophthalmic Surg Lasers Imaging Retina*. 2017;48(3):251-254.
24. Babu N, Kohli P, Ramasamy K. Comparison of various surgical techniques for optic disc pit maculopathy: vitrectomy with internal limiting membrane (ILM) peeling alone versus inverted ILM flap "plug" versus autologous scleral "plug." *Br J Ophthalmol*. 2020;104(11):1567-1573.
25. Ozdek S, Ozdemir HB. A new technique with autologous fibrin for the treatment of persistent optic pit maculopathy. *Retina Cases Brief Rep*. 2017;11(1):75-78.
26. Almeida DRP, Chin EK, Arjmand P, et al. Fibrin glue and internal limiting membrane abrasion for optic disc pit maculopathy. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49(12):e271–e277.
27. Caporossi T, D'Amico G, Tartaro R, et al. Optic disk pit maculopathy treatment using a human amniotic membrane patch: one-year results. *Am J Ophthalmol*. 2022;240:30-36.
28. Ooto S, Mittra RA, Ridley ME, et al. Vitrectomy with inner retinal fenestration for optic disc pit maculopathy. *Ophthalmology*. 2014;121(9):1727-1733.



**DAVID BOYER, MD**

- Senior Partner, Retina-Vitreous Associates Medical Group, Los Angeles
- Editorial Advisory Board Member, *Retina Today*
- vitdoc@aol.com
- Financial disclosure: None

**DANIEL SU, MD**

- Associate, Retina-Vitreous Associates Medical Group, Los Angeles
- dsu@laretina.com
- Financial disclosure: None

eyetube

# THE LATEST FROM EYETUBE

## CLINICAL MINUTE RETINA

*Ramin Tadayoni, MD, and guests discuss the latest research and clinical studies in retina.*

LATEST VIDEO

**Why Some Clinical Trials Succeed Where Others Do Not**

*Ramin Tadayoni, MD, PhD, and Peter Kaiser, MD*

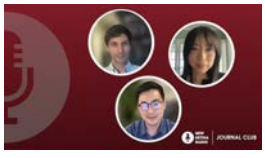
## NEW RETINA RADIO | JOURNAL CLUB

*This series is dedicated to reviewing the latest journal articles and how they relate to day-to-day clinical practice in retina.*

LATEST VIDEO

**Multifocal, Indolent, Nonprogressive Choroidal Lesions**

*Kyle D. Kovacs, MD; Cynthia Qian, MD; and David Xu, MD*



## NEW RETINA RADIO

*New Retina Radio is a place to hear stories about retina that are told nowhere else.*

LATEST PODCAST EPISODE

**ASRS Meeting Coverage Day 3: DR Biomarkers and Gene Tx for Achromatopsia**

*Jennifer Lim, MD, and Lejla Vajzovic, MD*

# FIVE WAYS iOCT CAN ENHANCE VITREORETINAL SURGERY

These surgical scenarios can be safer and more efficient with the assistance of intraoperative OCT.

BY LEANNE M. CLEVENGER, MD, AND ALEKSANDRA V. RACHITSKAYA, MD, FASRS


OCT has had profound clinical implications since its invention in 1991.[1] Now, with the advent of the microscope-integrated platform, we see an increased use of intraoperative OCT (iOCT).[1,2] The PIONEER (531 eyes) and DISCOVER (837 eyes) studies provided surgeons with detailed information on the utility of iOCT in anterior and posterior segment surgeries.[3,4] DISCOVER's 3-year results showed that the use of iOCT during posterior segment surgery added valuable information in approximately 60% of cases and potentially altered surgical decision making in approximately 30% of cases, regardless of surgeon experience.[3] Here, we present an overview of five vitreoretinal surgical scenarios where iOCT can be helpful.

## SCENARIO NO. 1: VITREORETINAL INTERFACE DISORDERS

iOCT can help to modify surgical decision making because it can reveal either residual membranes or completion of the membrane peel—potentially avoiding incomplete treatment or unnecessary surgical maneuvers.[5]

Macular hole (MH) surgery performed with iOCT has been reported to yield a high single-surgery success rate. In a post-hoc analysis of the DISCOVER trial, single-surgery MH closure was achieved in 97.6% of cases, comparable to outcomes in eyes receiving pars plana vitrectomy and internal limiting membrane (ILM) peel without iOCT (87% to 97%).[5-7]

Analysis of the MH morphology after the iOCT-assisted ILM peel can reveal features capable of predicting better anatomic and functional outcomes.[8,9] For example, in a retrospective case series of MH patients who were evaluated with iOCT at the end of the ILM peel, patients with a large MH (> 400 µm) and the presence of a "hole-door" (vertical pillars of tissue projecting into the vitreous cavity after ILM peeling) or "foveal flap" (preoperative foveal flap that adhered to the hole edge after ILM peeling) configuration had significantly better final visual acuity and restoration of the external limiting membrane.[8]

A post-hoc analysis of eyes from the PIONEER trial undergoing full-thickness MH repair demonstrated that intraoperative decrease in MH volume, intraoperative changes in minimal width, and pre-incision minimal width were the strongest predictors for early MH closure.[9]

iOCT has been applied during epiretinal membrane (ERM) peeling to visualize the membrane and minimize the use of adjuvant dyes such as ICG, which can potentially be associated with retinal toxicity.[10-13] Other advantages of iOCT include being able to verify the absence of intraoperative full-thickness MHs or residual membrane in surgeries for ERM or vitreomacular traction, which might affect the tamponade choice (Figure 1).[14,15] iOCT can reveal remnant posterior vitreous cortex that is strongly adherent

## AT A GLANCE

- Data from the DISCOVER trial showed that using intraoperative OCT (iOCT) during posterior segment surgery added valuable information in roughly 60% of cases, regardless of surgeon experience.
- iOCT has been applied during epiretinal membrane peeling to visualize the membrane and minimize the use of adjuvant dye.
- iOCT can provide real-time feedback during vitreoretinal surgery, but more investigation is needed to determine its ability to affect outcomes.

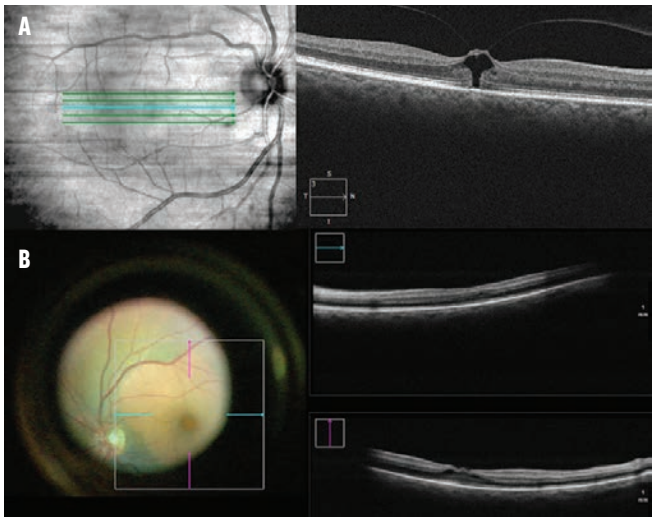



Image courtesy of Aleksandra V. Rachitskaya, MD, FASRS

Figure 1. The preoperative OCT image shows vitreomacular traction (A), and the iOCT confirmed a complete membrane peel without a residual full-thickness retinal defect (B).

to the retinal surface—particularly in highly myopic eyes with foveoschisis—and can reveal altered foveal architecture after the peel.[16,17]

Despite these advantages, further investigation is needed to understand the utility of iOCT to improve anatomical and functional outcomes, single-surgery success rate, and intraoperative efficiency.

## SCENARIO NO. 2: SUBMACULAR SURGERY

iOCT has been shown to be useful in subretinal bleb creation.[18,19] This becomes even more paramount in inherited retinal diseases where a bleb is created in the macula (Figure 2). Many patients with inherited retinal diseases have atrophic retinas, which can make it difficult to induce a localized detachment with balanced salt solution (BSS) or gene therapy product. iOCT can help to confirm that the injection occurs in the subretinal space, as opposed to damaging the underlying retinal pigment epithelium (RPE) or injecting into the sub-RPE space. With a BSS pre-bleb, iOCT can help localize the bleb retinotomy site and allow for optimal positioning of the subretinal cannula with gene product into the subretinal space. Following the delivery of the viral vector, iOCT can help to verify that a full-thickness MH did not develop.[18] In addition to visualizing the retinal architecture, novel research is measuring the volume of the bleb to determine the exact treatment delivered.[20]

Other subretinal pathology can be accessed with the assistance of iOCT, including subretinal PFO. iOCT can aid in visualizing subretinal PFO, confirming complete PFO removal, and ensuring there is no residual MH formation or other retinal defect.[21] In instances of submacular hemorrhage, iOCT can be useful in identifying optimal needle placement for the subretinal injection of tissue plasminogen activator, preventing intraretinal or sub-RPE injection.[22]

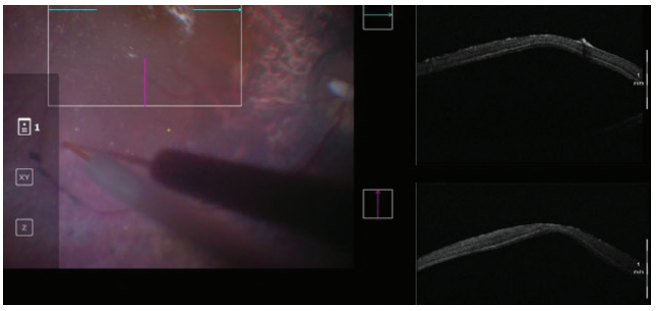


Image courtesy of Aleksandra V. Rachitskaya, MD, FASRS

Figure 2. When delivering subretinal gene product, iOCT is used to confirm foveal inversion with no MH formation.

**iOCT CAN REVEAL REMNANT POSTERIOR VITREOUS CORTEX THAT IS STRONGLY ADHERENT TO THE RETINAL SURFACE—PARTICULARLY IN PATIENTS WITH HIGHLY MYOPIC EYES WITH FOVEOSCHISIS.**

## SCENARIO NO. 3: PROLIFERATIVE DIABETIC RETINOPATHY

When operating on patients with proliferative diabetic retinopathy (PDR), there is often severely altered tissue anatomy that requires delicate manipulation and clear delineation of surgical planes. Common sight-threatening complications of diabetes in patients with PDR include nonclearing vitreous hemorrhage, tractional retinal detachments (RDs), combined rhegmatogenous and tractional RDs, or vitreomacular traction/ERMs. A review of patients who underwent surgery for the sequelae of PDR found that surgeons reported that iOCT provided valuable information in 50.6% of cases and altered surgical decision making in 26% of cases.[23] iOCT may be useful, especially in eyes with vitreous hemorrhage that could not be assessed with OCT preoperatively.[23,24] Moreover, in tractional RD cases it can be used during membrane peeling and assessment of surgical dissection planes. Other reported uses include visualization of cannula placement during viscodissection and in identifying peripheral or macular holes/breaks, guiding choice for tamponade agent.[23]

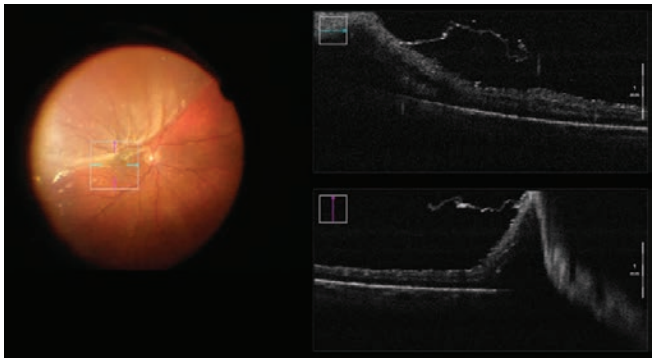


Image courtesy of Aleksandra V. Rachitskaya, MD, FASRS

**Figure 3. iOCT helped to identify an ERM during RD repair, which indicated the need for a membrane peel.**

## SCENARIO NO. 4: RHEGMATOGENOUS RD

In a post-hoc analysis of eyes undergoing RD repair in the DISCOVER study, iOCT was determined to provide valuable information to surgeons in 36% of cases.[25] Examples of helpful feedback included conformation of a posterior vitreous detachment, identification of residual subretinal fluid after PFO placement, confirmation of retinal reattachment, identification of the need for retinectomy, visualization of an occult MH, identification of a preretinal membrane, and identification of a retinal cyst (Figure 3).[25] The utility of feedback gained from iOCT was felt to be higher in complex RD repairs than with primary, noncomplex repairs (50% versus 22%, $P < .05$).[25] More investigation is needed to assess the outcomes of RD repair surgery with and without using iOCT.

## SCENARIO NO. 5: UVEITIS

In cases where an infiltrative condition such as malignancy, amyloidosis, or atypical infection is suspected, a chorioretinal biopsy may be warranted to obtain a definitive diagnosis.[26] iOCT can be useful in determining the site to biopsy and establishing if there is enough volume of subretinal material to allow for a successful biopsy.[26] In the DISCOVER study, iOCT affected the surgical procedure in five of seven eyes undergoing chorioretinal biopsy, mostly in helping to plan the biopsy location based on lesion size and site and for positioning the soft tip at the biopsy site.[27]

iOCT has been described as useful during the placement or replacement of the fluocinolone acetonide implant (Retisert, Bausch + Lomb), particularly for ensuring scleral wound integrity and closure at the implant site.[27] This can be critical when operating on eyes that have undergone multiple prior procedures, resulting in scleral thinning.[27]

## MORE TO DO

iOCT can provide real-time feedback during vitreoretinal surgery and can assist with surgical decision making. More investigation is needed to determine the tool's ability to improve patient outcomes in prospective, randomized clinical trials. ■


1. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254(5035):1178-1181.
2. Pujari A, Agarwal D, Chawla R, Kumar A, Sharma N. Intraoperative optical coherence tomography guided ocular surgeries: critical analysis of clinical role and future perspectives. *Clin Ophthalmol*. 2020;14:2427-2440.
3. Ehlers JP, Modi YS, Pecen PE, et al. The DISCOVER study 3-year results: feasibility and usefulness of microscope-integrated intraoperative oct during ophthalmic surgery. *Ophthalmology*. 2018;125(7):1014-1027.
4. Ehlers JP, Dupps WJ, Kaiser PK, et al. The prospective intraoperative and perioperative ophthalmic imaging with optical coherence tomography (PIONEER) study: 2-year results. *Am J Ophthalmol*. 2014;158(5):999-1007.
5. Yee P, Sevgi DD, Abraham J, et al. IOCT-assisted macular hole surgery: outcomes and utility from the DISCOVER study. *British J Ophthalmol*. 2021;105(3):403-409.
6. Jaycock PD, Bunce C, Xing W, et al. Outcomes of macular hole surgery: implications for surgical management and clinical governance. *Eye*. 2005;19(8):879-884.
7. Bae K, Kang SW, Kim JH, Kim SJ, Kim JM, Yoon JM. Extent of internal limiting membrane peeling and its impact on macular hole surgery outcomes: a randomized trial. *Am J Ophthalmol*. 2016;169(2013):179-188.
8. Tao J, Chen H, Zhu L, et al. Macular hole edge morphology predicts restoration of postoperative retinal microstructure and functional outcome. *BMC Ophthalmol*. 2020;20(1):1-7.
9. Ehlers JP, Uchida A, Srivastava SK, Hu M. Predictive model for macular hole closure speed: Insights from intraoperative optical coherence tomography. *Transl Vis Sci Technol*. 2019;8(1):18.
10. Ehlers JP, Khan M, Petkovsek D, et al. Outcomes of intraoperative OCT–assisted epiretinal membrane surgery from the PIONEER study. *Ophthalmol Retina*. 2018;2(4):263-267.
11. Lorusso M, Micelli Ferrari L, Gisotti EN, et al. Success of iOCT in surgical management of ERM peeling. *Eur J Ophthalmol*. 2022;32(5):3116-3120.
12. Rodrigues EB, Meyer CH, Mennel S, Farah ME. Mechanisms of intravitreal toxicity of indocyanine green dye: implications for chromovitrectomy. *Retina*. 2007;27(7):958-970.
13. Sakamoto T, Itaya K, Noda Y, Ishibashi T. Retinal pigment epithelial changes after indocyanine green-assisted vitrectomy. *Retina*. 2002;22(6):794-796.
14. Tuifua TS, Sood AB, Abraham JR, et al. Epiretinal membrane surgery using intraoperative OCT-guided membrane removal in the DISCOVER study versus conventional membrane removal. *Ophthalmol Retina*. 2021;5(12):1254-1262.
15. Ehlers JP, Tam T, Kaiser PK, Martin DF, Smith GM, Srivastava SK. Utility of intraoperative optical coherence tomography during vitrectomy surgery for vitreomacular traction syndrome. *Retina*. 2014;34(7):1341-1346.
16. Bruyère E, Philippakis E, Dupas B, Nguyen-Kim P, Tadayoni R, Couturier A. Benefit of intraoperative optical coherence tomography for vitreomacular surgery in highly myopic eyes. *Retina*. 2018;38(10):2035-2044.
17. Itoh Y, Inoue M, Kato Y, Koto T, Hirakata A. Alterations of foveal architecture during vitrectomy for myopic retinoschisis identified by intraoperative optical coherence tomography. *Ophthalmologica*. 2019;242(2):87-97.
18. Gregori NZ, Lam BL, Davis JL. Intraoperative use of microscope-integrated optical coherence tomography for subretinal gene therapy delivery. *Retina*. 2019;39:S9-S12.
19. Vasconcelos HM, Lujan BJ, Pennesi ME, Yang P, Lauer AK. Intraoperative optical coherence tomographic findings in patients undergoing subretinal gene therapy surgery. *Int J Retina Vitreous*. 2020;6(1):1-10.
20. Hsu ST, Gabr H, Viehland C, et al. Volumetric measurement of subretinal blebs using microscope-integrated optical coherence tomography. *Transl Vis Sci Technol*. 2018;7(2):19.
21. Smith AG, Cost BM, Ehlers JP. Intraoperative OCT-assisted subretinal perfluorocarbon liquid removal in the DISCOVER study. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46(9):964-966.
22. Ehlers JP, Petkovsek DS, Yuan A, Singh RP, Srivastava SK. Intrasurgical assessment of subretinal tPA injection for submacular hemorrhage in the PIONEER study utilizing intraoperative OCT. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46(3):327-332.
23. Khan M, Srivastava SK, Reese JL, Shwani Z, Ehlers JP. Intraoperative OCT-assisted surgery for proliferative diabetic retinopathy in the DISCOVER study. *Ophthalmol Retina*. 2018;2(5):411-417.
24. Tao J, Wu H, Chen Y, et al. Use of iOCT in vitreoretinal surgery for dense vitreous hemorrhage in a chinese population. *Curr Eye Res*. 2019;44(2):219-224.
25. Abraham JR, Srivastava SK, K Le T, et al. Intraoperative OCT-assisted retinal detachment repair in the DISCOVER study: impact and outcomes. *Ophthalmol Retina*. 2020;4(4):378-383.
26. Browne AW, Ehlers JP, Sharma S, Srivastava SK. Intraoperative optical coherence tomography-assisted chorioretinal biopsy in the DISCOVER study. *Retina*. 2017;37(11):2183-2187.
27. Kumar JB, Ehlers JP, Sharma S, Srivastava SK. Intraoperative OCT for uveitis-related vitreoretinal surgery in the DISCOVER study. *Ophthalmol Retina*. 2018;2(10):1041-1049.



**LEANNE M. CLEVENGER, MD**

- Vitreoretinal Surgery Fellow, Cole Eye Institute, Cleveland Clinic, Cleveland
- leanneclevenger@gmail.com; Twitter @ClevengerMD
- Financial disclosure: None

**ALEKSANDRA V. RACHITSKAYA, MD, FASRS**

- Vitreoretinal Surgery Physician, Cole Eye Institute, Cleveland Clinic, Cleveland
- Associate Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine, Cleveland
- Editorial Advisory Board Member, *Retina Today*
- rachita@ccf.org
- Financial disclosure: Consultant (Alcon, Carl Zeiss Meditec, Genentech/Roche, Regeneron); Research (AGTC, Apellis, Genentech/Roche, NGM Bio); Speakers' Bureau (Apellis, Genentech/Roche, Regeneron)

# CURRENT AND FUTURE MANAGEMENT OF GEOGRAPHIC ATROPHY

**David Eichenbaum, MD; Carl Regillo, MD; and Lejla Vajzovic, MD**

The next year may see significant changes in the geographic atrophy (GA) treatment landscape, as two companies, Iveric Bio and Apellis Pharmaceuticals, have each submitted New Drug Applications to the FDA for novel therapies targeting the role of complement inhibition—albeit by different strategies. To set the stage for what may be a transformative time in the lives of individuals affected by GA secondary to dry AMD, YoungMD Connect invited a panel of noted retina specialists to offer perspective on the current clinical landscape, what it means to live with a GA diagnosis (Figure), and why the development pipeline offers hope for optimism.

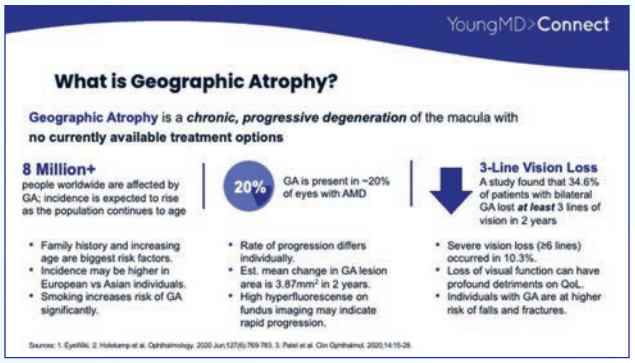



Figure. Fast facts about geographic atrophy.

## SETTING THE STAGE: THE PATIENT PERSPECTIVE

### David Eichenbaum, MD

**"It's a bit of a helpless feeling for the physician to have to explain the visual consequences of GA and then add that there are no currently available treatment options."**

- Consulting with GA patients can be very frustrating for the patient, for their family and support network, and for the physician.
  - The need for routine monitoring only compounds the burden and effects on daily living that patients with GA experience.
  - GA patients are typically older, and many need help attending their appointments, making GA a burden to the family and support network.
- Although vision loss associated with GA occurs late in the disease, it can be devastating. The slow progression of a central scotoma is something understood clinically, but for patients, it means the world is slowly disappearing before their eyes.
  - Referral to low vision services is an "underutilized service that definitely helps patients use their remaining vision more effectively."
- There is a definite knowledge gap around GA, and that can be a barrier.
  - The term geographic atrophy is not really used much in optometry or general ophthalmology practice, so when these patients get to the retina specialists, it may be the first time they are hearing the term.

## THE CURRENT LANDSCAPE: CLINICAL PERSPECTIVE OF GA

### Lejla Vajzovic, MD

**"The first complaint that our patients typically have is difficulty with night vision, which translates to difficulties with reading speed and doing activities they enjoy doing."**

- Patient-reported symptoms will lead the retina specialist to get an OCT or fluorescein angiography (FA); however, these practices may not be routinely used in general ophthalmology or optometric practices.
  - OCT coupled with infrared fundus photography is more common.
  - Autofluorescence is the best way to identify and understand the extent of GA.
- Referral to low vision specialists is key. These services help patients change their environment or give them tools to help them use their existing vision more effectively.
  - While loss of visual acuity (VA) is associated with GA, it is likely not the first symptom patients notice. Instead, patients often experience of loss of visual function (ie, difficulty reading, driving) as the first noticeable sign.
  - VA is not affected until the end stage of GA—typically when GA reaches the macula. The loss of VA in end-stage GA is sometimes referred to as "falling off the cliff."
- A number of ongoing clinical trials are testing new agents; some may pan out while others may not work—does talking about them offer hope or potentially false promises?
  - Dr. Vajzovic believes that mentioning ongoing clinical trials as part of the education process may be worthwhile. Her institution does a lot of research, so bringing up clinical trials is partly about increasing enrollment; at the same time, offering hope about what is coming in the pipeline may get patients to buy in to the need for monitoring.

## THE FUTURE IS BRIGHT: A LOOK DOWN THE INNOVATION PIPELINE

### Carl Regillo, MD

**"We're pushing the boulder uphill. The new agents in the pipeline represent significant progress and, if they make it to the clinic, would be meaningful for patients and their families."**

- There are agents in the pipeline that have demonstrated an ability to reduce the rate of growth of GA, which could delay the time to vision loss.
  - As well, a reduction in a central scotoma might help the patient use low vision aides more effectively and for longer.
- Complement inhibition is the only strategy that has demonstrated therapeutic effect in GA in clinical trials; some of the key ones to be aware of:
  - C3 blocker - APL-2 (pegcetacoplan; Apellis)
    - Intravitreally injected; in phase 3 trials, pegcetacoplan reduced GA lesion growth compared to sham and demonstrated a favorable safety profile. It is currently being reviewed by the FDA.
  - C5 blocker - aptamer - Zimura (avacincaptad pegol; Iveric Bio)
    - Studied in GATHER 1 and 2 trials.
    - Recently released data showed a statistically significant reduction in mean rate of growth in GA area with a favorable safety profile.
  - Both of these agents have demonstrated small effects from a clinical perspective, but they are nonetheless significant: any improvement would be meaningful in the context of current unmet need.
  - Both phase 3 studies used an anatomic endpoint, and no studies in GA have shown an effect on VA to date.
    - It is important to note that VA loss associated with GA typically occurs late in the disease process.
- Several previous attempts at developing GA therapies have failed; the history of those programs may be important to understand for those ophthalmologists who may interact with GA patients in their clinic.

**To gain access to educational workshops and advance your career, join the YoungMD Connect community.**

# MASTER THE VITREORETINAL BIOPSY BASICS

These techniques can help you reach a definitive diagnosis, even for tough cases unresponsive to treatment.

BY ABEL HAMDAN, MD; DANNY A. MAMMO, MD; AND SUNIL K. SRIVASTAVA, MD



Vitreoretinal surgeons can obtain tissue for diagnostic identification in several ways, depending on the suspected etiology. Examination of aqueous and vitreous specimens is the mainstay of diagnosis for inflammatory, neoplastic, and infectious ocular diseases, given the ease of sampling and the low risk of complications. However, more advanced approaches may be necessary for certain cases or in the event the vitreous sampling is inconclusive. Here, we discuss the benefits of various biopsy techniques, including fine needle aspiration biopsy (FNAB) and retinal/choroidal biopsies, and the surgical steps to obtain high-quality specimens.

## VITREOUS BIOPSY

Vitreous sampling continues to be a mainstay diagnostic method for inflammatory diseases affecting the posterior segment.[1] Vitreous can be obtained via pars plana vitrectomy (PPV) or FNAB, which are usually performed as primary procedures and, theoretically, have a lower risk profile than retinal/choroidal biopsies.[1]

When obtained with PPV, a vitreous sample is collected with aspiration into a syringe through a broken aspiration line while the cutter is activated.[1]

FNAB involves the insertion of a needle (attached to a syringe) at the pars plana; this method is not recommended for primarily vitreous aspiration, but could be a reasonable option for subretinal, sub-retinal pigment epithelium (RPE), or choroidal biopsy.[1]

Vitreous samples are often collected in an undiluted form for cytology and a diluted form for flow cytometry; vitreous can also be used for ancillary diagnostic techniques such as polymerase chain reaction (MYD88 or viral), cytokine rearrangement, metagenomic sequencing, and microbial/fungal microscopy and culture.[2,3] Cells removed from the vitreous are prone to rapid degeneration; thus, surgeons should promptly fixate or place the cells in a tissue culture and communicate with a cytopathologist.[1]

Postoperative complications of vitreous biopsy include false negative results, hemorrhage, retinal detachment, needle tract seeding, and endophthalmitis.[1]

## RETINAL/CHOROIDAL BIOPSIES

Retinal and choroidal biopsies have been shown to provide diagnostic answers in cases of inconclusive vitreous sample analyses.[1-8] Additionally, false negative vitreous studies are possible, with definitive diagnoses later confirmed using retinal/choroidal biopsies.[2,4,6,9] Specific cases where retinal/choroidal biopsies could be considered include retinal, subretinal, or choroidal lesions unresponsive to therapy with inconclusive initial testing. One of the most common indications for a retinal/choroidal biopsy is atypical uveitis unresponsive to treatment, especially when a rare neoplastic or infectious etiology is suspected.[2,4]

### Biopsy Steps

Many internal and external approaches exist for obtaining retinal and/or choroidal biopsies.[2,4] Surgeons can choose to cut/aspirate with a vitrector, perform a bimanual dissection of a lesion using scissors and forceps, or perform an FNAB

## AT A GLANCE

- Retinal and choroidal biopsies have been shown to provide diagnostic answers in cases of inconclusive vitreous sample analyses.
- Tissue biopsies may be performed with a vitrector, bimanual dissection, or fine needle aspiration.
- Surgeons should promptly fixate or place biopsied cells in a tissue culture and communicate with a cytopathologist.

through the pars plana using a 25- or 30-gauge needle.[1-3]

PPV with tissue dissection of the retina/choroid begins with a vitreous sample and is followed by these steps:

- Perform a complete vitrectomy followed by endodiathermy of retinal vessels surrounding the biopsy area and delineation of the biopsy site with a diode laser and/or full-thickness diathermy.
- Use curved horizontal scissors, vertical scissors, pneumatic vertical scissors, or a small-gauge vitreous cutter to cut through the retina and choroid.
- After dissecting a large enough target specimen, leave a small segment of the retina attached at the base to ensure the tissue is not lost due to fluidic changes.
- Make or extend a full-thickness sclerotomy.
- Use forceps (grasping at the base of the tissue site) to remove the specimen through the sclerotomy. You can also use a fluted, large-bore needle attached to suction or a syringe to extract the tissue.
- If needed, encircle the biopsy site with additional endolaser and tamponade with long-acting gas or silicone oil.[1]

When performing direct aspiration biopsy with the cutter, we identify the three thickest parts of the lesion, ideally away from large vessels. We raise the IOP to help prevent hemorrhage, introduce the cutter at a low cut rate, and aspirate the tissue, either directly into a syringe or into the tubing and then refluxed into a syringe. Complications of these approaches include cataract, retinal detachment, vitreous hemorrhage, choroidal hemorrhage, proliferative vitreoretinopathy, and endophthalmitis.[1]

FNAB of posterior choroidal tumors is often completed using a transvitreal approach, following these steps:

- Attach a 25- or 30-gauge needle, with tubing, to a syringe and introduce it through the pars plana at a meridian with the best accessibility to the tumor.
- Guide the needle into the tumor with either indirect ophthalmoscopy or a microscope, while avoiding major retinal or tumor vessels.
- Gently aspirate and withdraw the needle along the path of insertion.

Indirect ophthalmoscopy should be performed post-aspiration to search for any signs of trauma or hemorrhage. Localized hemorrhage can be addressed with targeted pressure; globe softening can be remedied with injection of balanced salt solution into the vitreous.[3,7]

There are many key aspects to note when considering FNAB. Ophthalmic FNAB has a high degree of diagnostic accuracy, although aspirated samples can be jeopardized by insufficient cellularity. Thus, a negative cytologic diagnosis should not exclude possible intraocular malignancy.[3] FNAB is also not recommended for the primary goal of obtaining vitreous, as getting a sufficient sample may be difficult. Still, FNAB is a reasonable option for diagnosis of a large subretinal, sub-RPE, or choroidal lesion. Again, priority should be given to prompt fixation or placement of samples into tissue culture.[1] Postoperative complications of FNAB can include false negative biopsy, theoretical needle tract seeding, hemorrhage, retinal detachment, and endophthalmitis.[3,7,8]

External transscleral techniques were some of the earliest methods described but are rarely performed due to the risk of suprachoroidal hemorrhage and other serious complications. These techniques may still be advantageous for lesions located anterior to the equator near the ora.[1] The transscleral technique begins with a conjunctival peritomy

## VISUALIZATION TIPS

Ocular imaging is invaluable as a supplemental tool to help guide our approach. Whether we perform direct aspiration through a lesion or perform a dissection is determined by preoperative and/or intraoperative OCT, which is a crucial part of our surgical management.[1] For example, for cases with a predominant sub-retinal pigment epithelium (RPE) and/or choroidal component, we perform an aspiration biopsy with the vitreous cutter (Figure 1). In cases of full-thickness retinal involvement, we prefer a full-thickness tissue dissection (Figure 2).

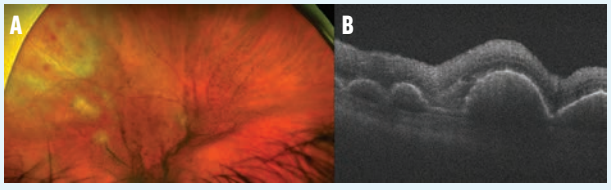



**Figure 1. An 82-year-old man presented with floaters and decreased vision in the right eye. Widefield imaging showed dense sheets and clumps of vitritis and temporal and superotemporal deep retinal whitening with intraretinal hemorrhages (A). Peripheral OCT over the lesion demonstrated inner retinal hyperreflectivity with subretinal hyperreflective material and a significant sub-RPE component to the lesion, making vitreoretinal lymphoma a likely diagnosis (B). Initial diagnostic PPV was performed without tissue biopsy due to the significant vitreous cells; it was negative on cytology and flow cytometry. Repeat surgery with tissue biopsy confirmed the diagnosis of vitreoretinal lymphoma. Due to the sub-RPE lesions, direct aspiration into the lesion with the cutter activated was the preferred method.**

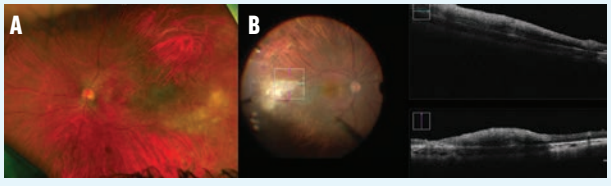



**Figure 2. A 49-year-old man presented with decreased vision in the left eye after a negative diagnostic vitrectomy at an outside institution. Widefield imaging demonstrated inferotemporal retinal whitening with associated intraretinal hemorrhages and far temporal hypopigmented deep retinal lesions (A). Macular RPE mottling was also present. Intraoperative OCT confirmed a predominantly full-thickness retinal lesion without any significant subretinal or sub-RPE component (B). A full-thickness retinal biopsy with manual dissection was performed, which was positive for large B-cell lymphoma.**

**EFFECTIVE COLLABORATION WITH CYTOPATHOLOGY CANNOT BE OVEREMPHASIZED TO MAXIMIZE POTENTIAL BIOPSY YIELD.**

and isolation of the rectus muscles. A nearly full-thickness scleral flap is created over the biopsy site, and diathermy is applied to the outer margin of the choroidal bed. A blade is then used to excise the specimen, and the flap is sutured back into place.[1]

## A MASQUERADER REVEALED

Intraocular lymphoma is a hallmark example of a masquerade syndrome that requires a definitive diagnosis to initiate proper treatment, yet it may initially respond to steroid therapy, making diagnosis difficult.[5] In these situations, vitreous biopsies, MRI brain studies, and lumbar punctures are often ordered but may still be inconclusive. Retinal or choroidal biopsy may provide the definitive diagnosis or exclude infectious or malignant diagnoses, enabling more targeted therapy.[2,4]

In our single-center retrospective study, 51 patients had diagnostic vitrectomies for suspicion of vitreoretinal lymphoma (VRL).[9] Of the 51 diagnostic vitrectomies, 39 were positive (76.5%) for VRL, 29 of which were vitreous positive. The remaining 10 positive biopsies (25%) were vitreous negative but retinal and/or subretinal biopsy (RSRB) positive. We performed a total of 14 RSRBs, and 13/14 (92%) were positive for VRL. Interestingly, 21 patients had retinal, subretinal, and/or sub-RPE lesions on initial visit, and 13 of these individuals (62%) had a negative vitreous biopsy, suggesting that eyes that present with clear lesions might have a lower cytopathological yield in the vitreous specimen.

The average time from symptom onset to diagnosis was 7.45 months among all patients. However, patients who tested positive only on RSRB tended to present later than patients with positive vitreous biopsies. Among RSRB positive but vitreous negative patients, the time to diagnosis was 8.56 months; for those with positive vitreous biopsy, the average time to diagnosis was 5.07 months ($P = .002$). There were no differences in vitreous haze scores between the groups.[9]

We hypothesize that by the time a lesion develops, the disease course is more chronic; given the fragility and necrosis of vitreous lymphocyte cells, the vitreous yield may decline with time. We obtained RSRBs through two different techniques: cutting/aspiration with a vitrector (10 cases) and bimanual dissection of a lesion using scissors and forceps (four cases). There were only two postoperative retinal detachments in the series, both from the cutting/aspiration group. These patients were attached after a follow-up PPV with gas tamponade.[9]

Thus, we highly consider RSRB for suspicious cases at the time of the primary diagnostic vitrectomy to expedite diagnosis and treatment.[9]

## BIOPSY IN OUR OR

Biopsy methods differ depending on surgeon experience and preference. We prefer a PPV approach due to comfort with the procedure and the desire for a definitive diagnosis at the time of the initial surgery. We also prefer a complete, rather than limited, vitrectomy to reduce the rate of false negative results, because inflammatory and lymphoma cells in the cortical vitreous have less chance to be sampled if a single core vitreous biopsy is performed.[1] When considering a biopsy site, it is important to note that the margins of lesions are more likely to harbor the pathologic process than the central lesion, which may be dominated by necrotic cells.[1] Likewise, effective collaboration with cytopathology cannot be overemphasized to maximize potential biopsy yield.[3] ■

1. Mastropasqua R, Di Carlo E, Sorrentino C, Mariotti C, da Cruz L. Intraocular biopsy and immunomolecular pathology for "unmasking" intraocular inflammatory diseases. *J Clin Med*. 2019;8(10):1733.
2. Lim LL, Suhler EB, Rosenbaum JT, Wilson DJ. The role of choroidal and retinal biopsies in the diagnosis and management of atypical presentations of uveitis. *Trans Am Ophthalmol Soc*. 2005;103:84-91.
3. Singh AD, Biscotti CV. Fine needle aspiration biopsy of ophthalmic tumors. *Saudi J Ophthalmol*. 2012;26(2):117-123.
4. Johnston RL, Tufail A, Lightman S, et al. Retinal and choroidal biopsies are helpful in unclear uveitis of suspected infectious or malignant origin. *Ophthalmology*. 2004;111(3):522-528.
5. Tang LJ, Gu CL, Zhang P. Intraocular lymphoma. *Int J Ophthalmol*. 2017;10(8):1301-1307.
6. Mastropasqua R, Thaung C, Pavesio C, et al. The role of chorioretinal biopsy in the diagnosis of intraocular lymphoma. *Am J Ophthalmol*. 2015;160(6):1127-1132.e1.
7. Mashayekhi A, Mazloumi M, Shields CL, Shields JA. Choroidal neovascular membrane after fine-needle aspiration biopsy of vitreoretinal lymphoma. *Retin Cases Brief Rep*. 2022;16(1):25-28.
8. Ebert JJ, Di Nicola M, Williams BK. Operative complications of posterior uveal melanoma surgery. *Internat Ophthalmol Clin*. 2022;62(3):15-33.
9. Srivastava SK, Mammo DA, Hamdan A. Vitreoretinal biopsy techniques and the role for retinal biopsy in vitreoretinal lymphoma: a single-institution experience. Presented at ASRS 2022; July 13-16, 2022; New York, New York.

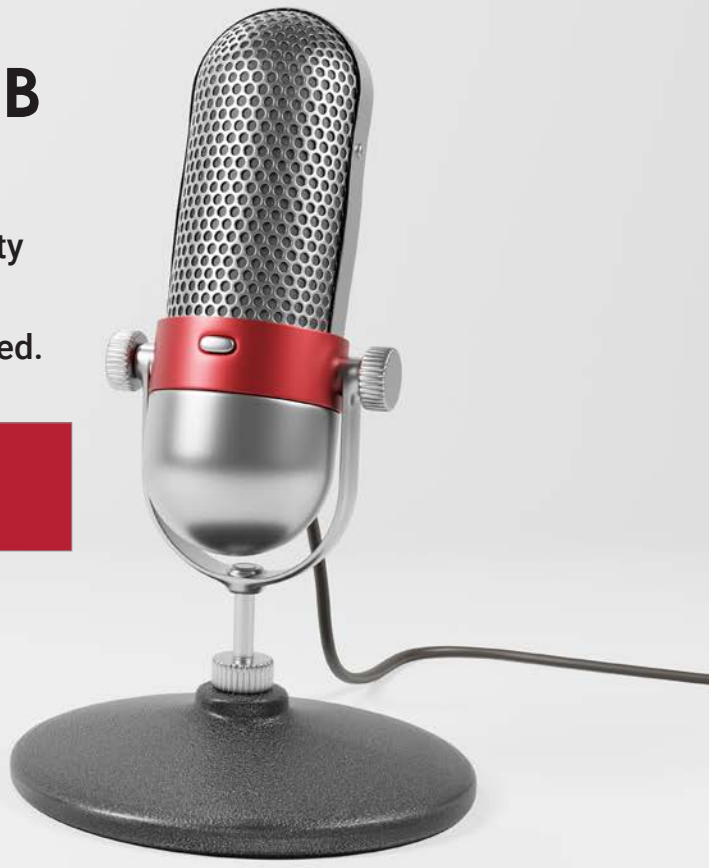
**ABEL HAMDAN, MD**
- Research Assistant, Cole Eye Institute, Cleveland Clinic, Cleveland
- hamdana3@ccf.org
- Financial disclosure: None

**DANNY A. MAMMO, MD**
- Vitreoretinal Surgery and Uveitis Specialist, Cole Eye Institute, Cleveland
- mammod@ccf.org
- Financial disclosure: Advisor (Alimera Sciences)

**SUNIL K. SRIVASTAVA, MD**
- Vitreoretinal Surgery and Uveitis Specialist, Cole Eye Institute, Cleveland
- srivass2@ccf.org
- Financial disclosure: Consultant (Adverum, Bausch + Lomb, Carl Zeiss Meditec, Eyepoint, Eyevensys, jCyte, Novartis, Regeneron); Research Grants (Eyepoint, Eyevensys, Regeneron)

Supported by Roche and Genentech
A Member of the Roche Group

# NEW RETINA RADIO | JOURNAL CLUB



New Retina Radio is partnering with the Vit-Buckle Society to provide quick-hit reviews of journal articles delivered by VBS members—all from the comfort of your podcast feed.

CATCH UP ON THE LATEST DISCUSSIONS AT
**eyetube.net/podcasts/new-retina-radio**

**RECENT TOPICS INCLUDE:**

Biosimilars in Retina
Stickler Syndrome and GRTs
Updates in ROP
Multifocal, Indolent, Nonprogressive Choroidal Lesions
Recurrent RRD Management

**HEAR FROM LEADING VITREORETINAL SURGEONS AND EXPERTS:**


Peter Campbell, MD


Karen Jeng-Miller, MD, MPH


Kyle Kovacs, MD


Yasha Modi, MD


Cynthia Qian, MD


Prethy Rao, MD


Katherine Talcott, MD


Ali Khan, MD


Priya Vakharia, MD


Basil Williams, MD


David Xu, MD


Yoshihiro Yonekawa, MD, PhD

*Learn more about the Vit-Buckle Society at www.vitbucklesociety.org*

***New Retina Radio** is available on Eyetube.net and through these platforms:*

Apple Podcasts | Google Podcasts | Spotify | STITCHER | iHeartRADIO

# CHROMOVITRECTOMY: A PRIMER

## An overview of different staining techniques, and a case to keep you on your toes.

BY PARNIAN ARJMAND, MD, MSC, FRCSC, DABO

The use of staining agents during vitreoretinal surgery, termed *chromovitrectomy*, can help surgeons visualize structures such as the internal limiting membrane (ILM) in full-thickness macular hole (FTMH) repair or the epiretinal membrane (ERM) while peeling. In addition to macular surgery, intraoperative staining agents can also be used to stain the posterior hyaloid to ensure the presence of a posterior vitreous detachment (PVD) or to visualize membranes in proliferative vitreoretinopathy.[1,2]

Here, I describe the characteristics of commonly used staining agents in macular surgery (Video), as well as a case of residual postoperative outer retinal triamcinolone acetonide particles in a patient who underwent uncomplicated MH surgery.

### DYE CHOICES

**Indocyanine green (ICG)** is a commercially available dye that comes in a powder form in a single vial of 25 mg lyophilized agent. Each vial is diluted with 10 mL of diluent fluid that accompanies the product to achieve a final concentration of 2.5 mg/mL. Some surgeons add an agent with a higher specific gravity, such as dextrose 5% in sterile water (D5W) or viscoelastic material, to allow for better staining of the ILM. To prepare ICG mixed with D5W, add 0.4 mL of D5W to the reconstituted ICG vial and gently swirl for a final ratio of 1:24 dextrose to ICG.

To prepare an ICG mixture with viscoelastic material, inject 0.5 mL balanced salt solution through the tip of the viscoelastic device syringe to prevent air bubbles when injecting the agent. Then, attach the tip of the 1 mL ICG dye syringe, which should contain an equal volume to the viscoelastic material, to the tip of the viscoelastic syringe. Moving the plunger with both hands in a back-and-forth motion, mix the two agents and transfer to one syringe.

ICG stains the ILM quite well and can also be used to visualize the ERM via "negative staining." Although this dye is widely used in North America and in other parts of the world, many in vitro studies have shown a dose- and time-dependent cytotoxic effect on the retinal pigment epithelium (RPE), and the clinical toxicity profile of ICG remains controversial.[1,3,4] Minimizing the duration of exposure to ICG (ideally less than 30 seconds), removing all residual dye from the vitreous cavity, and diluting the dye with D5W or viscoelastic can help minimize the risk of toxicity. Similarly, some evidence suggests an increased risk of phototoxic effects with endoillumination with ICG.[2-4] Minimizing direct foveal endoillumination can help mitigate the risk of long-term RPE damage.

**Triamcinolone acetonide (TA)** is a preservative-free steroid commonly used to stain the vitreous when inducing a PVD. Many surgeons also use TA to stain the ILM and/or ERM. TA 40 mg/mL can be used alone or diluted 1:4 in balanced salt solution. There is no known evidence of direct toxicity with this agent.

To use TA as a staining agent during macular surgery, first remove the steroid that was injected for PVD induction and reinject the product using a small amount to create a several

### AT A GLANCE

- Surgeons have several intraoperative staining agents to choose from, including indocyanine green (ICG), triamcinolone acetonide, brilliant blue G, and trypan blue.
- Although ICG is widely used, many in vitro studies have shown a dose- and time-dependent cytotoxic effect on the retinal pigment epithelium.
- Patients with residual triamcinolone acetonide on the fovea may often remain symptomatic with a subsequent scotoma in the immediate postoperative period.

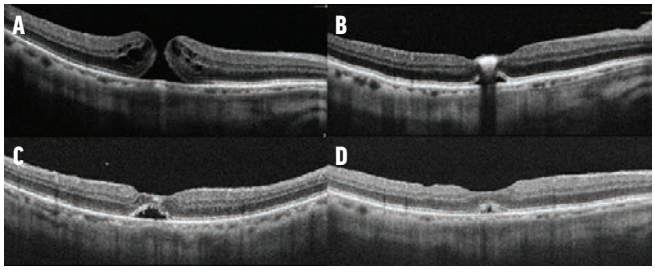



Figure 1. A preoperative OCT of the patient's right eye demonstrating a small FTMH (A). At 1 week postoperative, the OCT showed an intensely bright outer retinal hyperreflective lesion corresponding to TA particles on the fovea (B). The TA particle is smaller on OCT at week 3 postoperative with residual subretinal fluid (C). At month 2 postoperative, the TA residue is fully absorbed and the subretinal fluid is reduced significantly (D).

microns-thin layer of stain. This technique allows for optimal visualization of the retina under the stain and avoids inadvertent deep grabs or vascular nicking. The 27- or 30-gauge needle should be changed between each injection, as the emulsified product can clog the needle tip quickly. The assistant or scrub nurse should also be instructed to agitate the syringe well, and only prime the product seconds before injection.

Following ILM or ERM peel, remove all residual TA particulates from the vitreous. Although this product is safe, there is a hypothetical risk of postoperative sterile endophthalmitis, and residual steroid may delay MH closure.

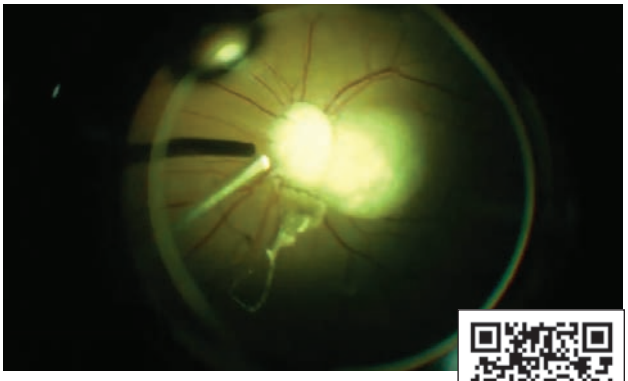
**Brilliant blue G (BBG)** is a commercially available dye at a 0.025% concentration that is FDA-approved to stain the ILM. Although not as efficacious as ICG, BBG is considered safer with reduced risks of cytotoxic damage to the RPE. Like ICG, BBG can also be mixed with D5W. Several authors have suggested better final visual acuity with the use of BBG over other macular staining agents, with no added advantage in rates of MH closure.[5,6]

**Trypan blue** is another commercially available dye at a 0.15% concentration and is commonly used in anterior segment surgery to stain the lens capsule. This dye can also be used to stain the ILM in MH surgery, as well as the ERM in proliferative vitreoretinopathy or diabetic membranes.

## CASE EXAMPLE

A 67-year-old man presented with a 3-month history of right eye distortion and blurry vision with baseline VA of 20/70 OD. He was phakic with 1+ nuclear sclerotic cataract and no past ocular or medical history. His OCT demonstrated a small FTMH in the right eye (Figure 1A), and he underwent uncomplicated combined phacovitrectomy in the right eye 1 month later. In this case, intravitreal TA was used to stain the posterior hyaloid, which was tightly adherent to the optic nerve and macula. Following PVD induction, a few residual triamcinolone crystals were noted. BBG was used to stain the ILM, which was peeled circumferentially without any complications. Following a complete fluid-air exchange, the eye was flushed with

WATCH IT NOW



Video. Improving Visualization with Triamcinolone Acetonide, ICG, and Trypan Blue

**ALTHOUGH NOT AS EFFICACIOUS AS INDOCYANINE GREEN, BRILLIANT BLUE G IS CONSIDERED SAFER WITH REDUCED RISKS OF CYTOTOXIC DAMAGE TO THE RETINAL PIGMENT EPITHELIUM.**

20% $SF_6$ gas. The patient was instructed to assume a face-down position for 5 to 7 days while awake.

At postoperative week 1, the gas fill was 40%, and a small but highly reflective TA crystal was seen clinically and on OCT (Figure 1B). At 3 weeks postoperative, the patient noted a small central scotoma in the right eye, and the crystal particle was still visible as a hyperreflective outer retinal lesion on OCT imaging with a small amount of residual subretinal fluid (Figure 1C).

By 2 months postoperative, the TA residue had absorbed, but a small residual amount of subretinal fluid remained (Figure 1D). This patient's final VA improved to 20/30+1, and he no longer noted a scotoma in the right eye. Fundus autofluorescence did not show any evidence of RPE changes in the macula at 2 months follow-up.

*(Continued on page 58)*

# RISING STARS IN RETINA

Get to know outstanding retina fellows from the class of 2023.



## Meera D. Sivalingam, MD

**_Retina Today_: When did you first know that you wanted to become a retina specialist?**

My initial interest was sparked the year after medical school when I spent some time working with Jean Bennett, MD, PhD, at the University of Pennsylvania's Perelman School of Medicine. That's what planted the seed. But my interest was confirmed during my second year of residency after shadowing in the retina OR. After seeing the complexity and the variety of surgical interventions that you can perform as a retina specialist, I knew it was the right fit for me.

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

I am lucky to have many mentors at Wills Eye Hospital in Philadelphia. In particular, Yoshihiro Yonekawa, MD, has been an amazing mentor. He has fostered my love for pediatric retina and has always pushed me outside of my comfort zone—outside of most people's comfort zone—as a retina specialist. He brought me into the complex pediatric retina fold and fostered my medical and surgical retina skills.

Sonia Mehta, MD, has been a vital mentor, especially as a woman in the retina field. From the time I was a medical student, I always looked up to her as a retina specialist and as a woman at Wills Eye. She has always encouraged me to push myself and truly strive for excellence.

**_RT_: What has been one of the most memorable experiences of your fellowship thus far?**

The OR experience that we get in fellowship is second to none. We see an immense variety of pathology at a high volume. The progress we make as surgeons in such a short period of time is unbelievable. Here at Wills Eye, it's because of the 22 attendings who all operate with us. It's amazing to think about where we started in July of our first year to where we are now as second-year fellows preparing to start our careers.

**_RT_: What are you hoping to accomplish once you are in practice?**

I see myself being part of a busy, high-volume practice and seeing a lot of complex cases. I am also passionate about teaching and fostering the next generation of residents and fellows. I wouldn't be anywhere today without all the people who have helped me along the way. Finding a career that will allow me to teach fellows and residents is part of my long-term goal. Being involved in cutting-edge clinical research is also important and something I am looking to continue in my career. Of course, a focus on pediatrics will be part of my practice, thanks to the influence of Dr. Yonekawa.

### FIRST CAREER MILESTONE

Dr. Sivalingam has chosen to start her career as a vitreoretinal surgeon at Mid Atlantic Retina in Philadelphia.

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

Never be afraid to put yourself out there. There is no such thing as an unwarranted question. There will always be people and mentors looking to help you, so don't be afraid to reach out if you feel like you need support.

Retina can feel intimidating to get into, but don't let that dissuade you from entering one of the most amazing surgical fields. ■

**MEERA D. SIVALINGAM, MD**
- Vitreoretinal Surgery Fellow, Wills Eye Hospital, Mid Atlantic Retina, Thomas Jefferson University, Philadelphia
- msivalingam@midatlanticretina.com
- Financial disclosure: None

CODING ADVISOR
A Collaboration Between *Retina Today* and AMERICAN ACADEMY™ OF OPHTHALMOLOGY Protecting Sight. Empowering Lives.

# DEBUNKING COMMON RETINA CODING MYTHS

These tips can help to ensure your claims are correct to avoid post-payment audits.

BY JOY WOODKE, COE, OCS, OCSR

Periodically, a colleague may provide you with coding advice. Perhaps the guidance is followed by statements like, "We have always billed this way. We get paid and have never been audited." So, it must be correct, right? No. Just because a claim was paid does not mean it is correct or not subject to a post-payment audit or recoupment. Here are a few myths and the real facts to be aware of.

## MYTH: All Payers Will Accept the Same Code for Bevacizumab Injections.

**Fact:** Each Medicare Administrative Contractor (MAC) has its own unique policies or articles related to intravitreal injection of bevacizumab (Avastin, Genentech/Roche). Thus, they all have varied health care common procedure coding system (HCPCS) codes to report the medication. For example, Novitas, Noridian, and First Coast Service Option require the code J7999, whereas Palmetto GBA and National Government Services accept J9035.[1] Others use unlisted or not otherwise classified HCPCS codes J3490 or J3590.

The Medicare Advantage, commercial, and Medicaid plans may have their own unique policies and requirements for reporting bevacizumab that are not the same as the local MAC. The Medicare Advantage plans often follow similar policies as their commercial counterparts and may even require prior authorization.

## MYTH: Office Visits That Determine the Need for Retinal Detachment Surgery Are Always an E/M Level 5.

**Fact:** It is true that when a macula-on retinal detachment is diagnosed and emergency surgery is scheduled in the near term (eg, within 24 hours), the overall medical decision making (MDM) would be high. The problem is high—an acute problem with a threat to bodily function—and risk is high when determining emergency major surgery.

However, not all retinal detachment surgery is scheduled as an emergency. For chronic retinal detachment or (often) retinal detachment with proliferative vitreoretinopathy, scheduling may be deferred to the next available appointment. In this case, the surgery would be considered a moderate MDM and an emergency and management (E/M) level 4.

## MYTH: It Is Always Appropriate to Unbundle 92134 (Posterior Segment OCT) and 92250 (Fundus Photography) When There Are Two Separate Diagnosis Codes.

**Fact:** Current procedural terminology (CPT) codes 92134 and 92250 have a National Correct Coding Initiative bundle with an indicator of 1, which means there may be circumstances that warrant unbundling. Some payers have published policies with guidance on when to unbundle, including Novitas local coverage determination L35038 and Palmetto local coverage article A56825.[1]

These two policies state that these two tests are generally mutually exclusive on the same day, but there may be a limited number of scenarios (eg, seperate indications for each test) when both are medically necessary. One example could be OCT for diabetic macular edema and fundus photography for a choroidal lesion. Appending modifier -59 would indicate a distinct procedure service. The

## For more tips and tricks, check out *Retina Today*'s Coding Advisor online:

**Three Questions When Coding Laser Therapy**
Lasers are a great tool in the retina clinic–just make sure you know how to properly code for them.

**Protect Your Revenue**
Take the coding quiz and test your expert coding knowledge.

**Mastering Modifier -24**
A breakdown of how you should code unrelated care during the surgical global period.

**How to Ace Internal Chart Audits**
Eliminate these five documentation deficiencies to ensure optimal reimbursement.

guidance notes that frequently unbundling may trigger a focused medical review.

In the absence of a payer policy that has published the unique conditions that warrant unbundling, it is best to bill only for the test that best supports the MDM during the encounter.

### MYTH: Always Bill the Examination on the Same Day as an Intravitreal Injection as an E/M Level 4.

**Fact:** The first step is to determine if it is appropriate to bill the examination on the same day as the minor procedure, meeting the definition of modifier -25. While medically necessary, if the examination is performed solely to confirm the need for the injection, it is not separately billable.

If the examination is billable with modifier -25, identify the reason for the significant, separately identifiable evaluation. For example, for an initial injection of the left eye for bilateral disease, the problem would be moderate complexity, chronic illness with progression, and moderate risk due to the prescription drug management of an anti-VEGF agent. For this case, the overall MDM is moderate and a level 4 E/M code.

When confirming the need for the injection in one eye along with the medically necessary examination of the fellow eye, the reason for the examination and MDM would be determined based on the reason for the fellow eye examination. For example, if it is a 4-month evaluation of stable dry AMD and the intent is to evaluate again in a few months, the problem and risk would be low, resulting in an overall low MDM and a level 3 E/M code.

**IN THE ABSENCE OF A PAYER POLICY THAT HAS PUBLISHED THE UNIQUE CONDITIONS THAT WARRANT UNBUNDLING, IT IS BEST TO BILL ONLY FOR THE TEST THAT BEST SUPPORTS THE MDM DURING THE ENCOUNTER.**

### MYTH: It is Best to Bill Eye Visit Codes Because They Pay More and Are Easier to Document.

**Fact:** With the 2021 revision to E/M documentation guidelines—the medically relevant history, examination, and final determination is based on MDM or total physician time—there are scenarios where E/M can be easier to document. Additionally, there was an increase in the relative value unit value of office-based E/M in 2021. In some cases, E/M has a higher reimbursement than the Eye Visit code.

For example, when it is determined during a new patient evaluation that the patient needs a vitrectomy at the next available appointment, this visit would be considered a new patient E/M level 4 with the CPT code 99204. Along with the moderate level of problem, there is a decision to perform a major surgery. If considering only Eye Visit codes, CPT code 92004 has a lower relative value unit and allowable than the E/M code for the comprehensive eye examination.

It is best to review the documentation and determine the level of E/M and Eye Visit code based on their unique documentation guidelines. You can then compare the allowable per the payer fee schedule to appropriately maximize reimbursement.

Visit aao.org/retinapm for more retina coding resources and review the 2023 Retina Coding: Complete Reference available at aao.org/store. More guidance on E/M coding can be accessed at aao.org/em. ■

1. Local coverage determination policies. AAOE Practice Management. Accessed December 19, 2022. aao.org/lcds

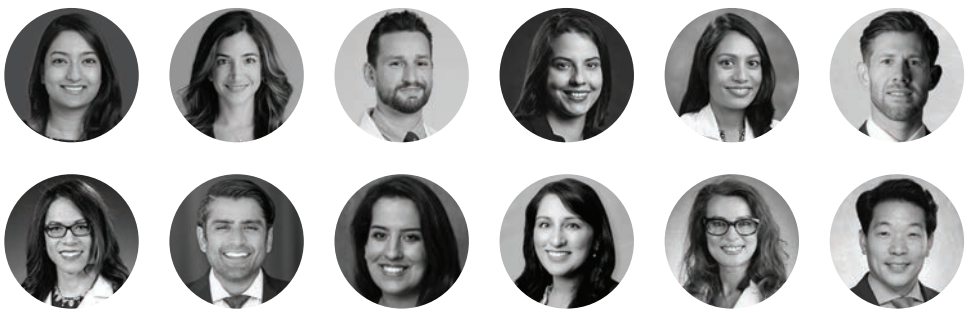
**JOY WOODKE, COE, OCS, OCSR**
- Director of Coding & Reimbursement, American Academy of Ophthalmology, San Francisco
- jwoodke@aao.org
- Financial disclosure: None

YoungMD > Connect

# Unparalleled Access to Thought Leaders in Retina

*Calling all trainees and new-to-practice ophthalmologists:*

Participate in monthly mentoring sessions & enjoy unequaled access to retina thought leaders and *peer mentors*.



***Sruthi Arepalli, MD***
***Parnian Arjmand, MD***
***Jordan Deaner, MD***
***Parisa Emami, MD***

**Avni Finn, MD**
***Eric Hansen, MD***
**Vivienne S. Hau, MD**
**Arshad Khanani, MD**

**Geeta Lalwani, MD**
**Sonia Mehta, MD**
**Dimitra Skondra, MD**
**Elliott Sohn, MD, FASRS**

**Scan the QR code for 20% off one-year membership (less than $30).**

*Discount automatically applied.*

**YoungMD Connect Members Gain Exclusive Access To:**

- ✔ **MENTORING SESSIONS** to build connections with thought leaders.
- ✔ **EDUCATIONAL WORKSHOPS** to complement your clinical training.
- ✔ ***BOOKMARKED* EDITORIAL FORUM** to read the latest articles in eye care.
- ✔ **RESOURCES** to build new skills.
- ✔ **JOB BOARD** to land your first job or make a change.
- ✔ **IN-PERSON EVENTS** to fasttrack your networking opportunities and engage with industry.

*YMDC is made possible with industry support from:*

VISIONARY: Allergan an AbbVie company · Johnson & Johnson VISION

FOUNDATIONAL: Apellis · Dompé · LUMIBIRD MEDICAL

PARTNER: Vision Innovation PARTNERS

GUIDING: Genentech A Member of the Roche Group · GLAUKOS TRANSFORMING VISION

*Brought to you by:* bmc vision · RT

# IDENTIFYING AMD OVERLAP SYNDROMES

Multimodal imaging can help to confirm AMD or AMD/CSCR overlap with challenging cases.

BY SAAGAR PANDIT, MD, MPH; ASAD F. DURRANI, MD; ANAND GOPAL, MD; AND LINNET RODRIGUEZ, MD

As imaging has advanced in the field of retina, so has our ability to distinguish various clinical entities such as wet AMD, polypoidal choroidal vasculopathy (PCV), and central serous chorioretinopathy (CSCR). Advances in spectral-domain OCT, OCT angiography (OCTA), fluorescein angiography (FA), ICG angiography (ICGA), and fundus autofluorescence (FAF) have made diagnosing these clinical entities easier and tracking treatment responses more manageable.

Here, we discuss how multimodal imaging can help differentiate classic wet AMD from PCV and CSCR.

## BASELINE IMAGING OF THE AMD SUSPECT

In addition to fundus photography, many other imaging tools are useful at the initial visit. Findings such as intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelial detachment (PED), and subretinal hyperreflective material (SHRM) on OCT can be used to monitor disease activity and determine when to initiate intravitreal injections and when to follow up with patients.[1]

OCT findings can also serve as biomarkers for visual outcomes. For example, the FLUID study demonstrated that patients administered ranibizumab (Lucentis, Genentech/Roche) on a treat-and-extend basis for an intensive fluid regimen (intolerance of both IRF and SRF) versus those on a relaxed fluid regimen (tolerance of SRF except for > 200 µm at the foveal center) had similar visual outcomes.[2]

Moreover, unique OCT findings can help identify patients with specific types of neovascularization. For example, one of the earliest signs of type 3 macular neovascularization (MNV) is a punctate hyperreflective focus above the external limiting membrane (ELM), anterior to a PED.[3] Additionally, the presence of a double-layer sign can be suggestive of PCV.[4]

FA is helpful for detecting and grading MNV and is particularly useful when distinguishing MNV secondary to AMD from entities such as CSCR or choroiditis.[5]

Classic CNV on FA is characterized by a well-demarcated area of hyperfluorescence appearing early and exhibiting progressive leakage. The border of the lesion can be intense with a central hypofluorescence. The lesion continues to leak into late phases, obscuring the boundaries of the lesion.

Occult CNV is characterized as either a fibrovascular PED or late leakage of an undetermined source. Fibrovascular PED has ill-defined areas of irregular elevation of staining/leaking with stippled hyperfluoresence. Late leakage of undetermined source is a less common form of occult CNV in which poorly defined areas of leakage appear at the level of RPE in the late phase.

Retinal angiomatous proliferation (RAP) can present as a combination of findings such as intraretinal leakage and/or hemorrhage and serous PED.[6]

The major constraint of FA is that it is time-consuming and has a rare, yet life-threatening side effect of anaphylaxis.

OCTA can directly visualize type 1 MNV without using intravenous dyes. A literature review found that the incidence of conversion to exudation, as documented with OCTA, ranged between 20% and 80% (between 6 months and 2 years).[7] One of the studies found that patients with dry AMD identified on OCTA in one eye and wet AMD in the other eye demonstrated approximately an 18-fold increased risk of subsequent exudation.[8]

Limitations to OCTA include movement artifacts,

the need for clear media, and difficulties detecting flow beneath PEDs.[9]

Indocyanine green has a greater binding affinity to plasma proteins than fluorescein and is associated with minimal leakage through the fenestrated choriocapillaris, allowing better visualization of the choroid than with FA. This may be useful for detecting MNV beneath macular hemorrhage and for distinguishing between AMD and PCV.[4]

FAF is particularly useful in monitoring geography atrophy, which corresponds to a hypoautofluorescent lesion within the macula. Specific patterns on FAF can correlate with changes in visual acuity that do not result from MNV.[10] In addition, FAF is useful in distinguishing atrophic lesions other than AMD, such as acquired vitelliform lesions.

## FOLLOW-UP IMAGING

At subsequent visits, multimodal imaging is often not a requirement unless the diagnosis of AMD remains in question. If it is, further imaging can help. Most retina specialists would agree that every visit should involve OCT because of its greater sensitivity for monitoring MNV activity compared with clinical examination. Patients with an increase in retinal thickness greater than 10% compared with prior visits will likely have clinically significant disease activity.[3]

A lack of response to intravitreal anti-VEGF therapy should raise suspicion for other etiologies such as CSCR, drusenoid PED, and acquired vitelliform lesions. Additional imaging, such as enhanced-depth imaging OCT can help to identify focal choroidal vascular dilation, thickening, subretinal fibrosis, and choroidal neovascularization, all of which can be found in chronic CSCR.[11]

Depending on the scenario, a patient with dry AMD can be monitored with OCTA. Moreover, OCTA can evaluate sudden changes in visual acuity not explained by OCT alone.

ICGA can help to identify the slow filling of polyps and late leakage in patients suspected of having PCV. It can also identify classic choroidal hyperpermeability in patients with CSCR.

## AMD-OVERLAP SYNDROMES

When establishing the diagnosis of wet AMD, clinicians look for drusen and a relatively thin-to-normal choroidal thickness. Hemorrhage or exudation out of proportion with what is expected raises the possibility of PCV. PCV often presents with orange nodules on clinical examination or OCT features such as a peaked PED, sub-RPE ring-like lesions, and an adjacent double-layer sign.[12] ICGA remains the standard and can clearly demonstrate the classic polyps.

As for chronic CSCR, clinicians look for the absence of drusen, bilateral RPE changes, and in most cases, the absence of neovascularization on OCTA (Figure 1).

FAF may also be helpful to demonstrate guttering hypo- and hyperautofluorescent changes (Figure 2).

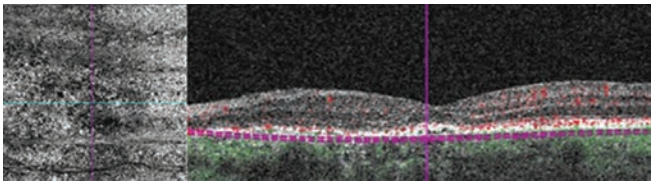


Figure 1. This patient was initially referred for wet AMD. OCTA of the left eye segmented at the level of the choriocapillaris demonstrated no neovascularization ( left). Adjacent flow overlay on the cross-sectional OCT imaging demonstrated no flow in the sub-RPE space (right). The patient was diagnosed with CSCR in each eye based on this imaging.

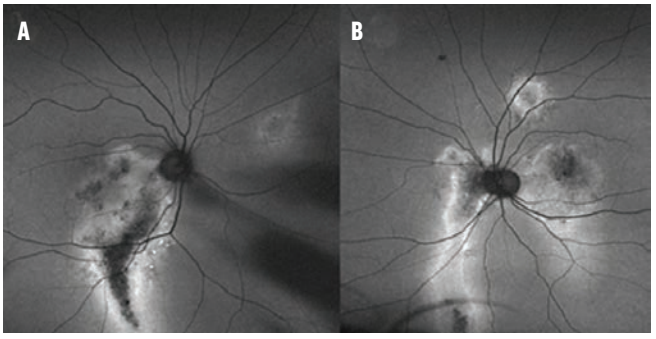



Figure 2. FAF of the right (A) and left eye (B) of the same patient in Figure 1 demonstrated characteristic hypo- and hyperautofluorescent "guttering" characteristic of multifocal chronic CSCR.

Type 1, 2, and 3 lesions on OCT correspond to occult, classic, and RAP lesions, respectively.[13] Additionally, OCT provides anatomic details of fluid location and whether there may be hemorrhage or fibrin corresponding with subretinal hyperreflective material.

## CASE STUDIES

Though rare, CSCR may coexist with exudative AMD, making it difficult to differentiate wet AMD from CSCR with or without CNV. Here we describe two cases involving CSCR and overlying AMD:

**Case No. 1:** A 78-year-old White man was referred for intermediate AMD in each eye. The fundus examination demonstrated intermediate drusen in each eye with pigmentary changes in the left eye greater than the right. The foveal cross-sectional OCT of the right eye demonstrated small drusenoid PEDs with subfoveal atrophy (Figure 3A). This was overlying a thickened choroid with enlarged or pachyvessels. The left eye's OCT demonstrated SRF in excess of what would be expected for wet AMD and a confluent row of PEDs forming a double-layer sign (Figure 3B). FAF showed the classic guttering consistent with chronic CSCR in the right and left eyes (Figure 3C). The early frame FA (Figure 3D, left) in the arteriovenous phase at 37 seconds and a later frame at 4 minutes and 12 seconds (right) showed subtle hyperfluorescence and leakage of a type 1 CNV and an "ink-blot" leakage consistent with CSCR.

**Case No. 2:** A 60-year-old White woman was referred for bilateral intermediate AMD. The fundus examination

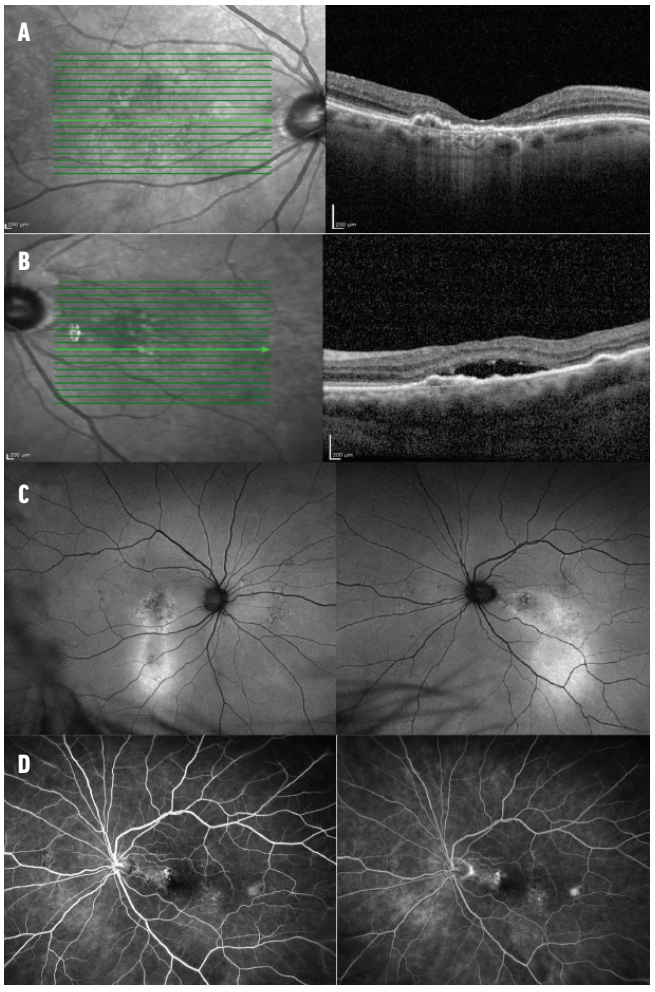



**Figure 3. OCT of the right (A) and left (B) eyes, FAF (C), and FA (D) showed clinical signs of chronic CSCR of the right eye and CSCR with indolent secondary type 1 neovascularization of the left eye superimposed on intermediate AMD.**

demonstrated intermediate drusen in each eye with pigment changes in the left eye and no hemorrhage. The foveal cross-sectional OCT of the right eye demonstrated small drusenoid PEDs (Figure 4A). The left eye demonstrated SRF in excess of what would be expected for wet AMD and a confluent row of PEDs forming a double-layer sign (Figure 4B). OCTA demonstrated type 1 neovascularization along the nasal margin of the PED (Figure 4C).

Both cases demonstrate the utility of multimodal imaging in confirming AMD/CSCR overlap, which would have been an otherwise difficult diagnosis to make. ■

1. Rosenfeld PJ. Optical coherence tomography and the development of antiangiogenic therapies in neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2016;57(9):14-26.
2. Guymer RH, Markey CM, McAllister IL, et al. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. *Ophthalmology*. 2019;126(5):723-734.
3. Nagiel A, Sarraf D, Sadda SR, et al. Type 3 neovascularization: evolution, association with pigment epithelial detachment, and treatment response as revealed by spectral domain optical coherence tomography. *Retina*. 2015;35(4):638-647.
4. Dansingani KK, Gal-Or O, Sadda SR, Yannuzzi LA, Freund KB. Understanding aneurysmal type 1 neovascularization (polypoidal choroidal vasculopathy): a lesson in the taxonomy of 'expanded spectra'–a review. *Clin Exp Ophthalmol*. 2018;46(2):189-200.
5. Holz FG, Sadda SR, Staurenghi G, et al. Imaging protocols in clinical studies in advanced age-related macular degeneration: recommendations from classification of atrophy consensus meetings. *Ophthalmology*. 2017;124(4):464-478.

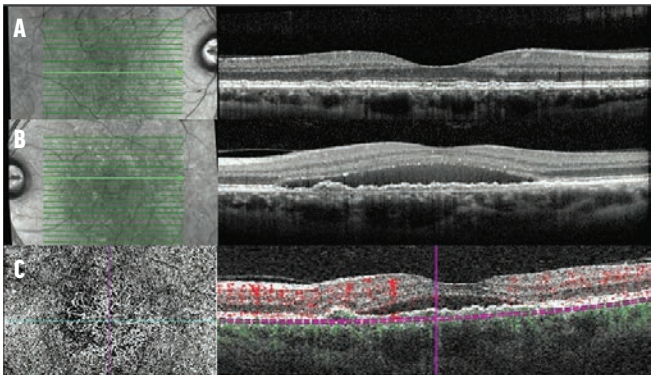



**Figure 4. OCT of the right (A) and left (B) eyes showed intermediate AMD of the right eye and CSCR with indolent secondary type 1 neovascularization of the left eye superimposed on intermediate AMD. OCTA with an en-face flow image using a slab with boundaries between the RPE and Bruch membrane demonstrated a type 1 neovascularization along the nasal margin of the PED (C).**

6. Domalpally A, Danis RP. Fluorescein angiography in neovascular AMD. *Rev Ophthalmol*. August 25, 2008. Accessed February 15, 2021. reviewofophthalmology.com/article/fluorescein-angiography-in-neovascular-amd
7. Laiginhas R, Yang J, Rosenfeld PJ, Falcão M. Nonexudative macular neovascularization – a systematic review of prevalence, natural history, and recent insights from OCT angiography. *Ophthalmol Retina*. 2020;4(7):651-661.
8. Bailey ST, Thaware O, Wang J, et al. Detection of nonexudative choroidal neovascularization and progression to exudative choroidal neovascularization using OCT angiography. *Ophthalmol Retina*. 2019;3(8):629-636.
9. Kuehlewein L, Bansal M, Lenis TL, et al. Optical coherence tomography angiography of type 1 neovascularization in age-related macular degeneration. *Am J Ophthalmol*. 2015;160(4):739-748.
10. Holz FG, Bindewald-Wittich A, Fleckenstein M, et al. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *Am J Ophthalmol*. 2007;143(3):463-472.
11. Ferrara D, Mohler KJ, Waheed N, et al. En face enhanced-depth swept-source optical coherence tomography features of chronic central serous chorioretinopathy. *Ophthalmology*. 2014;121(3):719-726.
12. Cheung CMG, Lai TYY, Teo K, et al. Polypoidal choroidal vasculopathy: consensus nomenclature and non-indocyanine green angiograph diagnostic criteria from the Asia-Pacific Ocular Imaging Society PCV Workgroup. *Ophthalmology*. 2021;128(3):443-452.
13. Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for choroidal neovascularization in age-related macular degeneration? *Retina*. 2010;30(9):1333-1349. Published correction appears in: *Retina*. 2011;31(1):208.

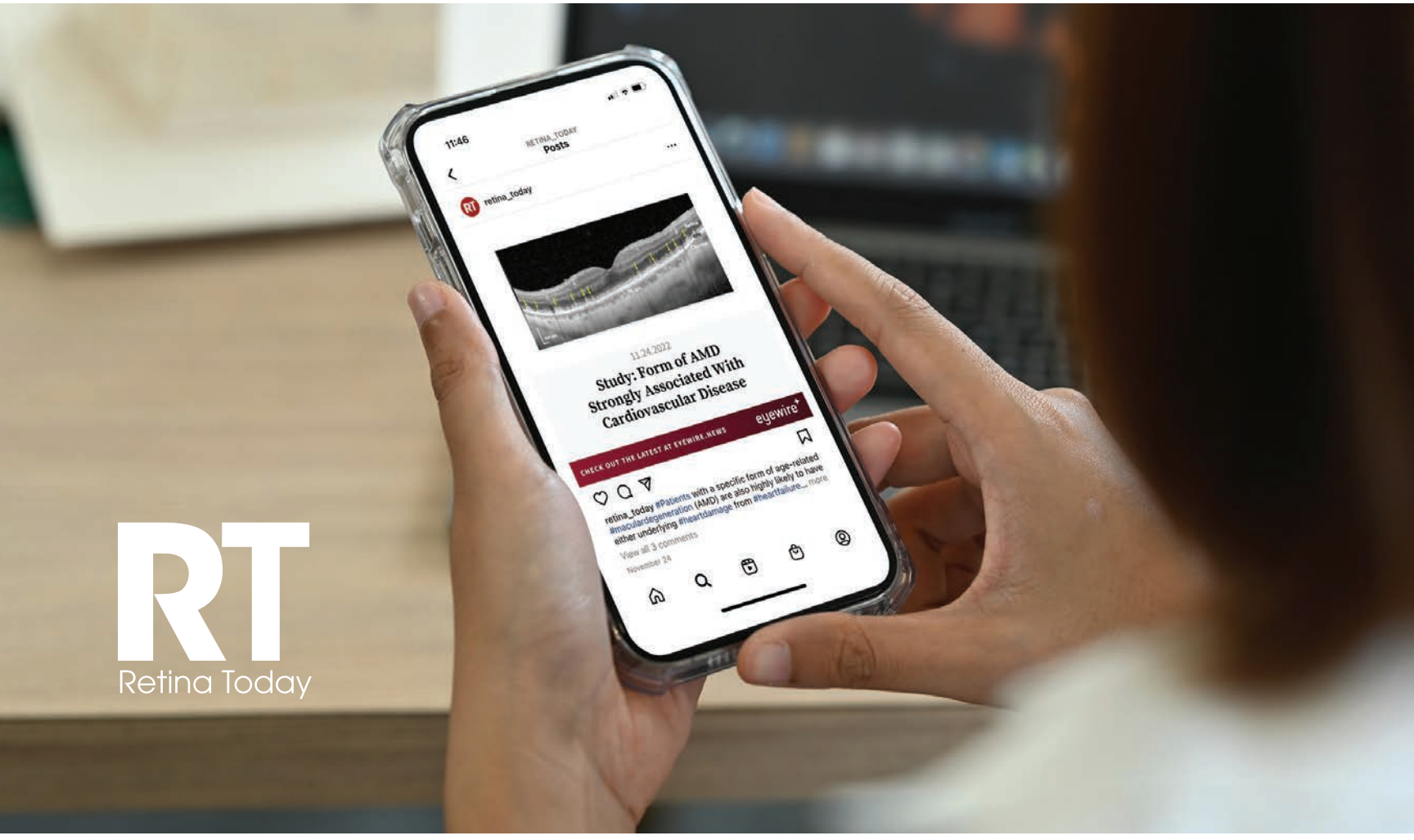
**SAAGAR PANDIT, MD, MPH**
- Vitreoretinal Surgery Fellow, Wills Eye Hospital Retina Service, Mid Atlantic Retina, and Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- saagar.pandit@gmail.com
- Financial disclosure: None

**ASAD F. DURRANI, MD**
- Vitreoretinal Surgery Fellow, Wills Eye Hospital Retina Service, Mid Atlantic Retina, and Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- adurrani@midatlanticretina.com
- Financial disclosure: None

**ANAND GOPAL, MD**
- Vitreoretinal Surgery Fellow, Wills Eye Hospital Retina Service, Mid Atlantic Retina, and Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- agopal@midatlanticretina.com
- Financial disclosure: None

**LINNET RODRIGUEZ, MD**
- Vitreoretinal Surgery Fellow, Wills Eye Hospital Retina Service, Mid Atlantic Retina, and Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- linrodriguez@midatlanticretina.com
- Financial disclosure: None

# JOIN US ON INSTAGRAM




Follow us for the latest surgical pearls and meeting insights straight from your peers.

**@retina_today**

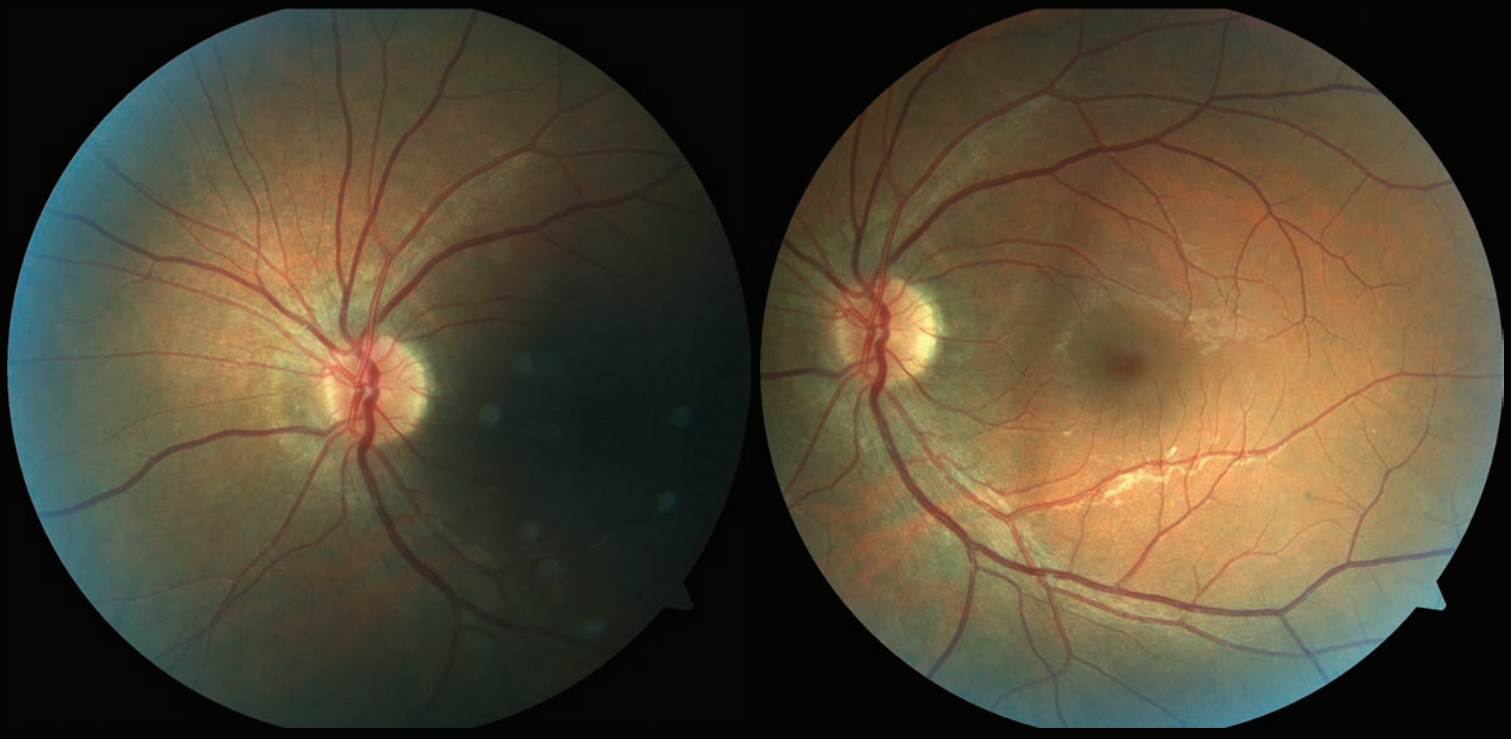


FIGURE 1

# THE CASE OF THE ENORMOUS BLIND SPOT

Learn to diagnose acute idiopathic blind spot enlargement syndrome.

BY ZURAB GLONTI, MD; SHALVA SKHIRTLADZE, MD; AND GIORGI MEKVABISHVILI, MD

A 30-year-old White man presented with loss of peripheral vision in his left eye for 1 week, photopsia, and awareness of a darkened area in this field of vision, all after a "flash bulb" sensation. His medical history was unremarkable other than LASIK surgery in his right eye 2 years earlier. His BCVA was 20/20 OU. There was a trace relative afferent pupillary defect 1+ in his left eye. The anterior segment was normal in each eye. The fundus examination of the right eye was normal, while the left eye had retinal pigment epithelium changes and circumpapillary subretinal grayish discoloration (Figure 1).

The map of the central 30° of the left eye's visual field, plotted 2 weeks after the vision loss, revealed an enormous blind spot (Figure 2). Spectral-domain OCT showed damage to the photoreceptors (ie, loss of ellipsoid zone [EZ]) in the nasal retina of the left eye. Fluorescein angiography arterial phase demonstrated a ring of circumpapillary hypofluorescence, filling the defect in the superior arcade (Figure 3).

## DIAGNOSIS AND FOLLOW-UP

Based on the symptomatology, examination findings, and imaging, we diagnosed the patient with acute idiopathic blind spot enlargement (AIBSE) syndrome. The patient was monitored without intervention.

Upon returning to the clinic 3 months later, his dilated fundus examination was unremarkable. Swept-source OCT imaging (Figure 4) showed minimal loss of the parafoveal EZ (1,460 µm of intact EZ from the foveal center at baseline vs 1,340 µm [Figure 4, inset] at 3 months). Further loss of EZ was limited to the part of the retina that had a relatively intact outer nuclear layer. There was no improvement; the condition remained stable at the 3-month follow-up.

FIGURE 2

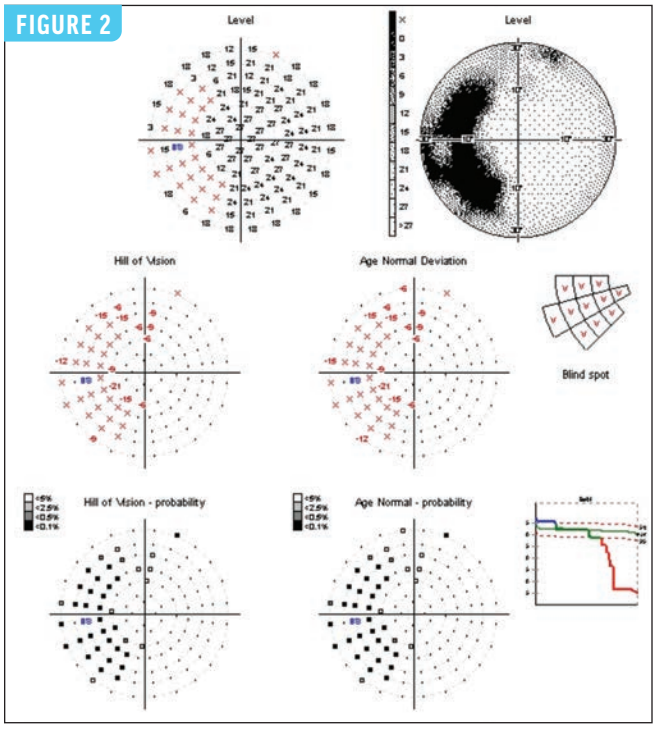
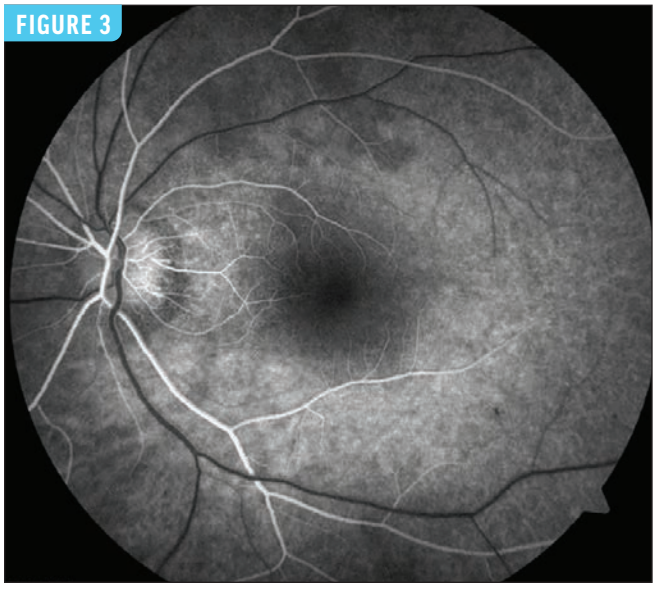


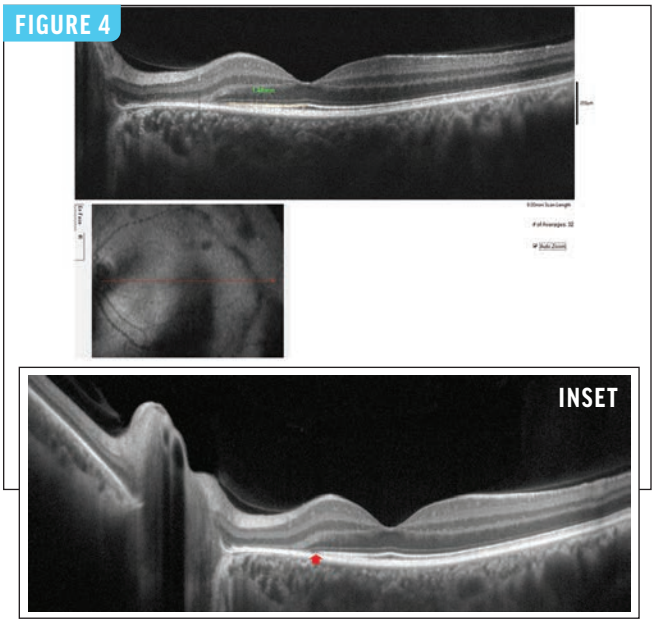

FIGURE 3



## DISCUSSION

AIBSE is a rare outer retinopathy that more commonly affects women. It has been postulated to present either as an isolated finding or as an entity of primary inflammatory choriocapillaropathies with circumscribed loss of outer retinal function. All races and ethnicities can be affected, with a higher incidence in White individuals and those with moderate-to-high myopia. AIBSE may also be a late manifestation of multiple evanescent white dot syndrome without the dots, although the penchant for the peripapillary retinal dysfunction suggests a local etiology.[1]

FIGURE 4




Treatment strategies for AIBSE syndrome remain unclear, and there are no preventative measures. The enlargement of the blind spot usually does not return to normal, and peripapillary scars may be observed. Moreover, residual photopsia and visual defects can occur. Rarely, the disease may recur.[2] ■

1. Jampol L, Wiredu A. MEWS, MFC, PIC, AMN, AIBSE, and AZOOR: one disease or many? *Retina*. 1995;15(5):373-378.
2. Doan A, Lee AG, Boldt HC. Acute zonal occult outer retinopathy (AZOOR) and acute idiopathic blind spot enlargement syndrome (AIBSE): 34-year-old female awoke with painless loss of vision OS 3 weeks prior to presentation. The University of Iowa Ophthalmology and Visual Sciences EyeRounds.org. February 21, 2005. Accessed December 9, 2022. eyerounds.org/cases/case18.htm

**ZURAB GLONTI, MD**
- Retina and Uvea Specialist, LTD Aversi Clinic, Tbilisi, Georgia
- zura_glonti@yahoo.com
- Financial disclosure: None

**GIORGI MEKVABISHVILI, MD**
- Retina Specialist and Neuro-Ophthalmologist, LTD Akhali Mzera, Tbilisi, Georgia
- Financial disclosure: None

**MANISH NAGPAL, MS, FRCS, FASRS | SECTION EDITOR**
- Senior Consultant, Retina and Vitreous Services, The Retina Foundation, Ahmedabad, India
- drmanishnagpal@yahoo.com
- Financial disclosure: Consultant (Nidek)

**SHALVA SKHIRTLADZE, MD**
- Vitreoretinal Surgery Fellow, Narayana Nethralaya Eye Hospital, Karnataka India
- Financial disclosure: None

**If you have an image or images you would like to share, email Dr. Nagpal.**
Note: Photos should be 400 dpi or higher and at least 10 inches wide.

*(Continued from page 47)*

## DISCUSSION

TA is one of the most commonly used agents in vitreoretinal surgery.[7] Despite its high safety profile, some case reports have noted TA crystals that have delayed or interfered with MH closure.[8,9] More recently, authors have reported larger case series and cohort studies with excellent anatomical and visual outcomes despite residual macular TA crystals.[7,10-12] Payne et al reported six cases of stage 3 and 4 FTMH in which residual TA crystals were seen inside the hole, touching the RPE, with no effect on MH closure or final visual acuity.[9] In our case, the TA crystal was on the outer surface of the retina and disappeared by 2 months, similar to the timeline reported by others.[7,10-12]

Although residual TA on the fovea is generally a benign postoperative finding, it is notable that patients may remain symptomatic with a subsequent scotoma in the immediate postoperative period. Our patient also developed persistent subretinal fluid postoperatively, which has been commonly noted in cases of small FTMH, with a longer time to recovery.[13,14] It is unclear whether the use of triamcinolone delays the absorption of postoperative subretinal fluid.

Retina surgeons benefit from an array of safe and efficacious staining agents in vitreoretinal surgery. Ultimately, the use of each staining agent for chromovitrectomy depends on factors such as agent availability and cost and surgeon preference. ■

1. Rodrigues EB, Meyer CH. Meta-analysis of chromovitrectomy with indocyanine green in macular hole surgery. *Ophthalmologica*. 2008;222(2):123-129.
2. Chromovitrectomy/ILM stain. ASRS Retina Atlas. Accessed November 27, 2022. atlas.asrs.org/article/chromovitrectomyilm-stain-84
3. Rodrigues EB, Meyer CH, Mennel S, Farah ME. Mechanisms of intravitreal toxicity of indocyanine green dye: implications for chromovitrectomy. *Retina*. 2007;27(7):958-970.
4. Gandorfer A, Haritoglou C, Kampik A. Toxicity of indocyanine green in vitreoretinal surgery. *Dev Ophthalmol*. 2008;42:69-81.
5. Azuma K, Noda Y, Hirasawa K, Ueta T. Brilliant blue G-assisted internal limiting membrane peeling for macular hole. *Retina*. 2016;36(5):851-858.
6. Jindal A, Pathengay A, Mithal K, Chhablani J, Pappura RR, Flynn HW. Macular toxicity following brilliant blue G-assisted macular hole surgery - a report of three cases. *Nepal J Ophthalmol*. 2014;6(11):98-101.
7. Wallsh J, Asahi MG, Gallemore R. Long-term outcomes of macular hole repair with triamcinolone acetonide visualization. *Clin Ophthalmol*. 2021;15:1607-1619.
8. Yamauchi Y, Nakamura H, Hayakawa K, Sawaguchi S. Persistence of triamcinolone acetonide following macular hole surgery. *Acta Ophthalmologica Scandinavica*. 2006;84(5):711-712.
9. Yeung CK, Chan KP, Chiang SWY, Pang CP, Lam DSC. The toxic and stress responses of cultured human retinal pigment epithelium (ARPE19) and human glial cells (SVG) in the presence of triamcinolone. *Invest Ophthalmol Vis Sci*. 2003;44(12):5293-5300.
10. Hikichi T, Furukawa Y, Ohtsuka H, et al. Improvement of visual acuity one-year after vitreous surgery in eyes with residual triamcinolone acetonide at the macular hole. *Am J Ophthalmol*. 2008;145(2):267-272.
11. Payne JF, Bergstrom C, Yan J, Aaberg Sr TM, Srivastava SK. Residual triamcinolone acetonide sequestered in the fovea after macular hole repair. *Retina*. 2011;31(1):148-153.
12. Kumar A, Sinha S, Gupta A. Residual triamcinolone acetonide at macular hole after vitreous surgery. *Indian J Ophthalmol*. 2010;58(3):232-234.
13. Tranos PG, Stavrakas P, Vakalis AN, Asteriadis S, Lokovitis E, Konstas AGP. Persistent subretinal fluid after successful full-thickness macular hole surgery: prognostic factors, morphological features and implications on functional recovery. *Adv Ther*. 2015;32(7):705-714.
14. Mehta N, Bhardwaj S, Tsui E, Tseng J, Wald K. Residual sub-retinal fluid after idiopathic macular hole repair surgery is not visually significant and resolves within 6 months. *Invest Ophthalmol Vis Sci*. 2016;57:1090.

**PARNIAN ARJMAND, MD, MSC, FRCSC, DABO**
■ Vitreoretinal Surgeon, Ophthalmologist, Toronto Retina Institute, Toronto
■ parnian.arjmand@medportal.ca
■ Financial disclosure: Speaker (Bayer, Sentrex)

# INDEX OF ADVERTISERS

**Apellis** ..... 9
www.apellis.com

**EyePoint Pharmaceuticals** ..... 5, 6
www.eyepointpharma.com

**Iridex** ..... 11
www.iridexretina.com

**Iveric Bio** ..... Cover 2
www.ivericbio.com

**MedOne Surgical** ..... 17
www.medone.com

**Notal Vision** ..... 25
www.notalvision.com

**Oculus** ..... 21
www.oculussurgical.com

**Regeneron** ..... 59, Cover 4
hcp.eylea.us

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

# EYLEA® (aflibercept) Injection For Intravitreal Injection

**BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.**

**1 INDICATIONS AND USAGE**
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

**Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).**

**4 CONTRAINDICATIONS**

**4.1 Ocular or Periocular Infections**
EYLEA is contraindicated in patients with ocular or periocular infections.

**4.2 Active Intraocular Inflammation**
EYLEA is contraindicated in patients with active intraocular inflammation.

**4.3 Hypersensitivity**
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Endophthalmitis and Retinal Detachments**
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

**5.2 Increase in Intraocular Pressure**
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

**5.3 Thromboembolic Events**
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

**6 ADVERSE REACTIONS**
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

**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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

**Neovascular (Wet) Age-Related Macular Degeneration (AMD).** The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

**Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies**

| | Baseline to Week 52 | | Baseline to Week 96 | |
|---|---|---|---|---|
| **Adverse Reactions** | **EYLEA (N=1824)** | **Active Control (ranibizumab) (N=595)** | **EYLEA (N=1824)** | **Control (ranibizumab) (N=595)** |
| Conjunctival hemorrhage | 25% | 28% | 27% | 30% |
| Eye pain | 9% | 9% | 10% | 10% |
| Cataract | 7% | 7% | 13% | 10% |
| Vitreous detachment | 6% | 6% | 8% | 8% |
| Vitreous floaters | 6% | 7% | 8% | 10% |
| Intraocular pressure increased | 5% | 7% | 7% | 11% |
| Ocular hyperemia | 4% | 8% | 5% | 10% |
| Corneal epithelium defect | 4% | 5% | 5% | 6% |
| Detachment of the retinal pigment epithelium | 3% | 3% | 5% | 5% |
| Injection site pain | 3% | 3% | 3% | 4% |
| Foreign body sensation in eyes | 3% | 4% | 4% | 4% |
| Lacrimation increased | 3% | 1% | 4% | 2% |
| Vision blurred | 2% | 2% | 4% | 3% |
| Intraocular inflammation | 2% | 3% | 3% | 4% |
| Retinal pigment epithelium tear | 2% | 1% | 2% | 2% |
| Injection site hemorrhage | 1% | 2% | 2% | 2% |
| Eyelid edema | 1% | 2% | 2% | 3% |
| Corneal edema | 1% | 1% | 1% | 1% |
| Retinal detachment | <1% | <1% | 1% | 1% |

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

**Macular Edema Following Retinal Vein Occlusion (RVO).** The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

**Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies**

| | CRVO | | BRVO | |
|---|---|---|---|---|
| **Adverse Reactions** | **EYLEA (N=218)** | **Control (N=142)** | **EYLEA (N=91)** | **Control (N=92)** |
| Eye pain | 13% | 5% | 4% | 5% |
| Conjunctival hemorrhage | 12% | 11% | 20% | 4% |
| Intraocular pressure increased | 8% | 6% | 2% | 0% |
| Corneal epithelium defect | 5% | 4% | 2% | 0% |
| Vitreous floaters | 5% | 1% | 1% | 0% |
| Ocular hyperemia | 5% | 3% | 2% | 2% |
| Foreign body sensation in eyes | 3% | 5% | 3% | 0% |
| Vitreous detachment | 3% | 4% | 2% | 0% |
| Lacrimation increased | 3% | 4% | 3% | 0% |
| Injection site pain | 3% | 1% | 1% | 0% |
| Vision blurred | 1% | <1% | 1% | 1% |
| Intraocular inflammation | 1% | 1% | 0% | 0% |
| Cataract | <1% | 1% | 5% | 0% |
| Eyelid edema | <1% | 1% | 1% | 0% |

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

**Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR).** The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

**Table 3: Most Common Adverse Reactions (≥1%) in DME Studies**

| | Baseline to Week 52 | | Baseline to Week 100 | |
|---|---|---|---|---|
| **Adverse Reactions** | **EYLEA (N=578)** | **Control (N=287)** | **EYLEA (N=578)** | **Control (N=287)** |
| Conjunctival hemorrhage | 28% | 17% | 31% | 21% |
| Eye pain | 9% | 6% | 11% | 9% |
| Cataract | 8% | 9% | 19% | 17% |
| Vitreous floaters | 6% | 3% | 8% | 6% |
| Corneal epithelium defect | 5% | 3% | 7% | 5% |
| Intraocular pressure increased | 5% | 3% | 9% | 5% |
| Ocular hyperemia | 5% | 6% | 5% | 6% |
| Vitreous detachment | 3% | 3% | 8% | 6% |
| Foreign body sensation in eyes | 3% | 3% | 3% | 3% |
| Lacrimation increased | 3% | 2% | 4% | 2% |
| Vision blurred | 2% | 2% | 3% | 4% |
| Intraocular inflammation | 2% | <1% | 3% | 1% |
| Injection site pain | 2% | <1% | 2% | <1% |
| Eyelid edema | <1% | 1% | 2% | 1% |

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

**6.2 Immunogenicity**
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
*Animal Data*
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

**8.2 Lactation**
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

**8.3 Females and Males of Reproductive Potential**
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

**8.4 Pediatric Use**
The safety and effectiveness of EYLEA in pediatric patients have not been established.

**8.5 Geriatric Use**
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

**17 PATIENT COUNSELING INFORMATION**
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
**Regeneron Pharmaceuticals, Inc.**
777 Old Saw Mill River Road
Tarrytown, NY 10591



Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.20.09.0052

# WHAT COULD THEY SEE THIS YEAR?

EYLEA® (aflibercept) Injection
For Intravitreal Injection

10 years & COUNTING
FDA approved 2011


*Inspired by real patients with Wet AMD, MEfRVO, and DME.*

- **First-line efficacy and safety data from 8 clinical trials[1]**
- **Dosing flexibility across several FDA-approved indications[1]**
- **>20 million doses administered to >1.6 million eyes since launch[2]**
- **Broad first-line coverage and dedicated support with EYLEA4U®[2]**

EXPLORE THE DATA
**at hcp.eylea.us**

## IMPORTANT SAFETY INFORMATION

## CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

## WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

## ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

## INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

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

**References: 1.** EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. June 2021. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

REGENERON®


777 Old Saw Mill River Road, Tarrytown, NY 10591 06/2022 EYL.22.05.0005