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Retina Today

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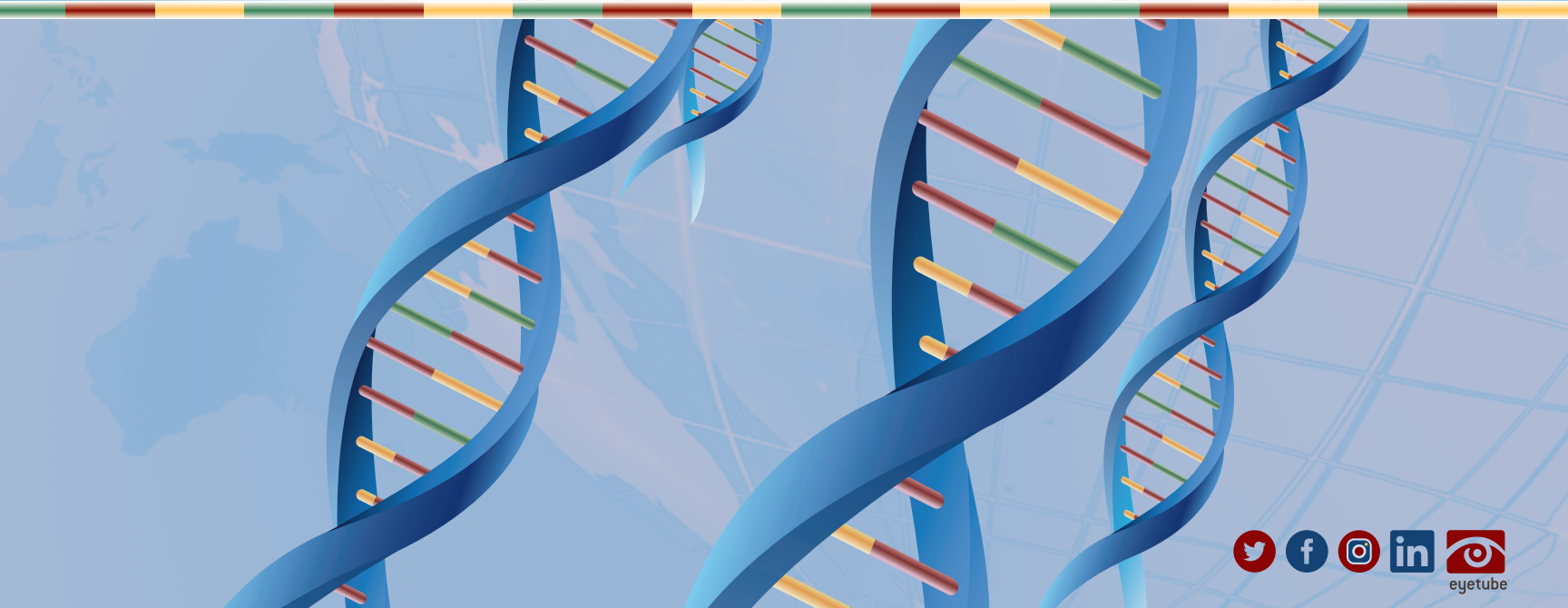
RARE AND INHERITED RETINAL DISEASES

International perspectives on challenging retinal conditions.



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IRDS AROUND THE WORLD

Guest Editors: Christine Kay, MD, and Aleksandra Rachitskaya, MD


There are disparities in health care access present in every country around the world. But sometimes, the contrast in access is stark, particularly in the case of rare conditions. In this issue, focused on rare and inherited retinal diseases (IRDs), we highlight the progress that has been made in genetic testing and IRD clinical trials. Hossein Ameri, MD, PhD, and Luciano C. Greig, MD, PhD, who are practicing in Los Angeles, note that identifying gene mutations has become a part of routine clinical care "thanks to the low cost and widespread availability of gene panel testing." (Check out *The Latest in Gene Therapy Clinical Trials for IRD* for their excellent rundown of the robust pipeline of therapeutics under investigation.)

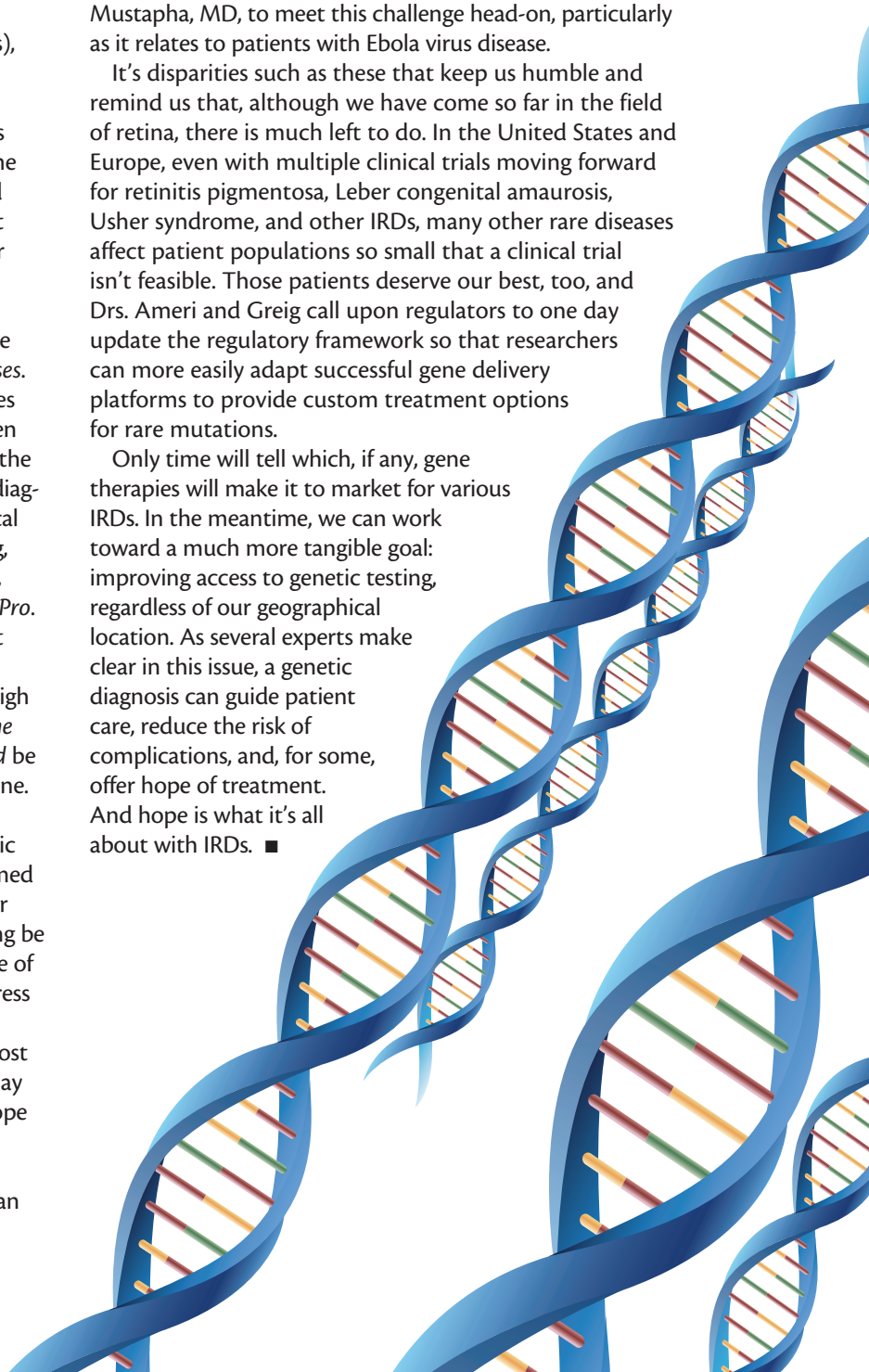
The examples of genetic testing used in clinical practice can be found in this issue's *Retina Detectives: Mystery Cases*. The article is a wonderful demonstration of the challenges of making a clinical diagnosis for IRDs—for example, when polled on social media, only 18% of retina specialists got the diagnosis correct for case no. 1. It's also fun to test your diagnostic acumen and look over some very interesting clinical images. If you want to know *how* to order genetic testing, Jennifer Huey, MS, CGC, and Debarshi Mustafi, MD, PhD, share their tips and tricks in *Order Genetic Testing Like a Pro*.

However, on the other side of the world, it's a different story. Paul Runge, MD, has been volunteering in Ukraine and was surprised to find himself treating an unusually high number of patients with IRDs (see *Global Retina Care: The Ukraine Experience*). He agrees that genetic testing *should* be routine, but it's neither widespread nor low cost in Ukraine. In fact, "there is no genetic testing available in our area, and I have had families travel to Italy or Poland for genetic testing," he explained in an interview. Now that a confirmed genetic diagnosis could provide access to a clinical trial or even treatment options, "it is essential that genetic testing be made available to our patients," he added. This is just one of many somewhat surprising hurdles he is working to address with Ukrainian colleagues.

In other countries, such as those in West Africa, the most advanced technology available for an eye examination may be only a vision chart, penlight, and direct ophthalmoscope (read more in *Global Retina Care: Uveitis in West Africa*). These tools are useful for identifying cataracts, corneal scarring, and other anterior segment findings, but they can limit a clinician's ability to diagnose early signs of another relatively rare group of conditions, different types of uveitis, which is prevalent in this population. Steven Yeh, MD, and Jessica G. Shantha, MD, MSc, have been working in Sierra Leone with Lloyd Harrison-Williams, MD, and Jalikatu Mustapha, MD, to meet this challenge head-on, particularly as it relates to patients with Ebola virus disease.

It's disparities such as these that keep us humble and remind us that, although we have come so far in the field of retina, there is much left to do. In the United States and Europe, even with multiple clinical trials moving forward for retinitis pigmentosa, Leber congenital amaurosis, Usher syndrome, and other IRDs, many other rare diseases affect patient populations so small that a clinical trial isn't feasible. Those patients deserve our best, too, and Drs. Ameri and Greig call upon regulators to one day update the regulatory framework so that researchers can more easily adapt successful gene delivery platforms to provide custom treatment options for rare mutations.

Only time will tell which, if any, gene therapies will make it to market for various IRDs. In the meantime, we can work toward a much more tangible goal: improving access to genetic testing, regardless of our geographical location. As several experts make clear in this issue, a genetic diagnosis can guide patient care, reduce the risk of complications, and, for some, offer hope of treatment. And hope is what it's all about with IRDs. ■



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- 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.

*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.

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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. February 2022. **2.** Data on file.

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Initial U.S. Approval: 1963

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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

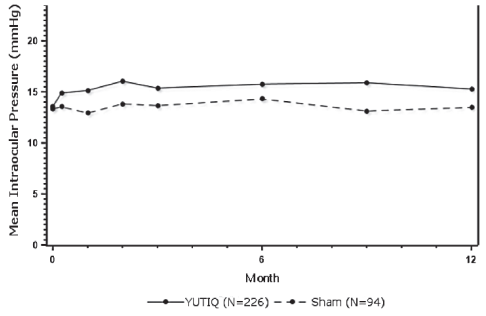
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
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.

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RT NEWS

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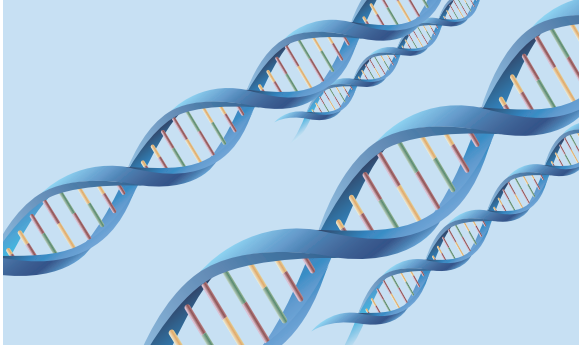

RESEARCHERS DETECT EARLY RETINAL NEURODYSFUNCTION IN PREDIABETES

Researchers in the United Kingdom used multimodal imaging to identify changes in the retinal neovascular structure of patients with prediabetes that precede the development of visible diabetic retinopathy (DR).[1] Their findings, published in *Diabetic Medicine*, suggest the potential benefit of updating the current glycemic thresholds for diagnosing diabetes, which are based on the detection of DR.

The cross-sectional analysis included 75 patients with normoglycemia (n = 20), prediabetes (n = 29), and type 2 diabetes (n = 26). Each patient underwent testing with OCT angiography (OCTA), handheld electroretinography (ERG), corneal confocal microscopy, and evaluation of electrochemical skin conductance. The latter two tests showed no difference between the normoglycemia and prediabetes groups. OCTA imaging revealed reduced parafoveal vessel densities in both the superficial and deep retinal layers in the prediabetes group. ERG demonstrated that the mean peak ERG amplitudes of retinal responses at low and high retinal illuminance were also lower in this group.

Together, these data suggest that neovascular pathology related to the onset of diabetes is detectable at an earlier stage than previously thought. The findings suggest that the presence of this early end-organ damage could help clinicians individualize the diagnostic thresholds for normoglycemia, prediabetes, and diabetes instead of relying on measures of hyperglycemia alone.[1] The team believes that OCTA and ERG could be easily adapted to screen patients with prediabetes.

1. Kirthi V, Reed KI, Alattar K, et al. Multimodal testing reveals subclinical neurovascular dysfunction in prediabetes, challenging the diagnostic threshold of diabetes. *Diabet Med*. 2023;40(3):e14952.

REGENERON ANNOUNCES 2-YEAR DATA

Two-year data from the PHOTON trial evaluating 8 mg aflibercept (Regeneron) for patients with diabetic macular edema (DME) showed that 89% of patients in the treatment arm maintained ≥ 12-week dosing and 83% maintained ≥ 16-week dosing over 2 years (compared with 93% and 89%, respectively, over 1 year).[1] In addition, 43% of patients met the criteria for ≥ 20-week intervals by week 96. Visual gains remained consistent with the first year of the trial.

The safety profile was on par with 2 mg aflibercept (Eylea, Regeneron) through 2 years. There were no cases of retinal vasculitis, occlusive retinitis, or endophthalmitis.

The FDA did not approve 8 mg aflibercept, citing "an ongoing review of inspection findings at a third-party filler."[2] The FDA did not report any issues with efficacy, safety, trial design, labeling, or drug manufacturing, the company said in a news release.[2]

1. Two-year results for aflibercept 8 mg from PHOTON Trial demonstrate durable vision gains at extended dosing intervals in DME [press release]. Eyewire+. June 27, 2023. Accessed July 5, 2023. eyewire.news/news/two-year-results-for-aflibercept-8-mg-from-photon-trial-demonstrate-durable-vision-gains-at-extended-dosing-intervals-in-dme
2. FDA does not approve Regeneron's high-dose aflibercept. Eyewire+. June 27, 2023. Accessed July 5, 2023. eyewire.news/news/fda-does-not-approve-regenerons-high-dose-aflibercept

RESEARCHERS UNCOVER THE POTENTIAL OF NEURONS TO HEAL CERTAIN VISION PROBLEMS

In the journal *Development*, researchers reported new insights into nerve cells, including a small population of cells that could be coaxed to regrow and potentially restore sight.[1]

It was initially thought that humans lacked the immature nerve cells necessary to regrow axons. However, according to the research team at the University of Connecticut School of Medicine, neurons exist that behave similarly to embryonic nerve cells; they express a similar subset of genes and can be experimentally stimulated to regrow long-distance axons. This could potentially lead to the healing of some vision problems caused by nerve damage.

Based on the results of this experimental axon regeneration, two of the particularly active genes in these neurons could be the target for future therapies. ■

1. New nerve insights could someday help heal certain types of blindness and paralysis. Eyewire+. June 9, 2023. Accessed July 5, 2023. eyewire.news/news/new-nerve-insights-could-someday-help-heal-certain-types-of-blindness-and-paralysis

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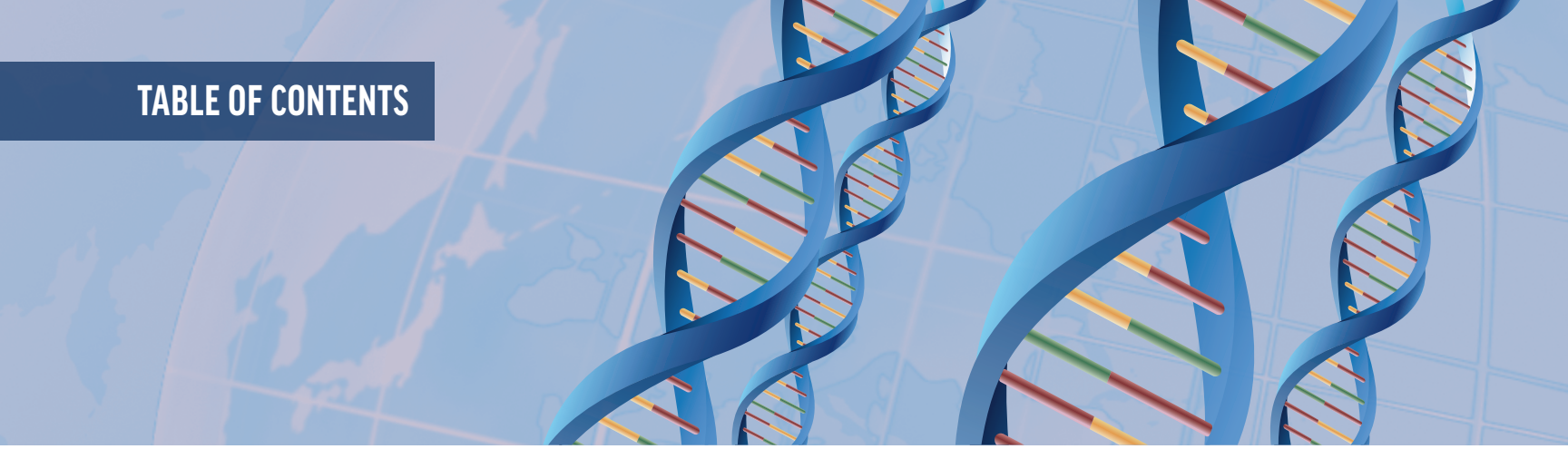

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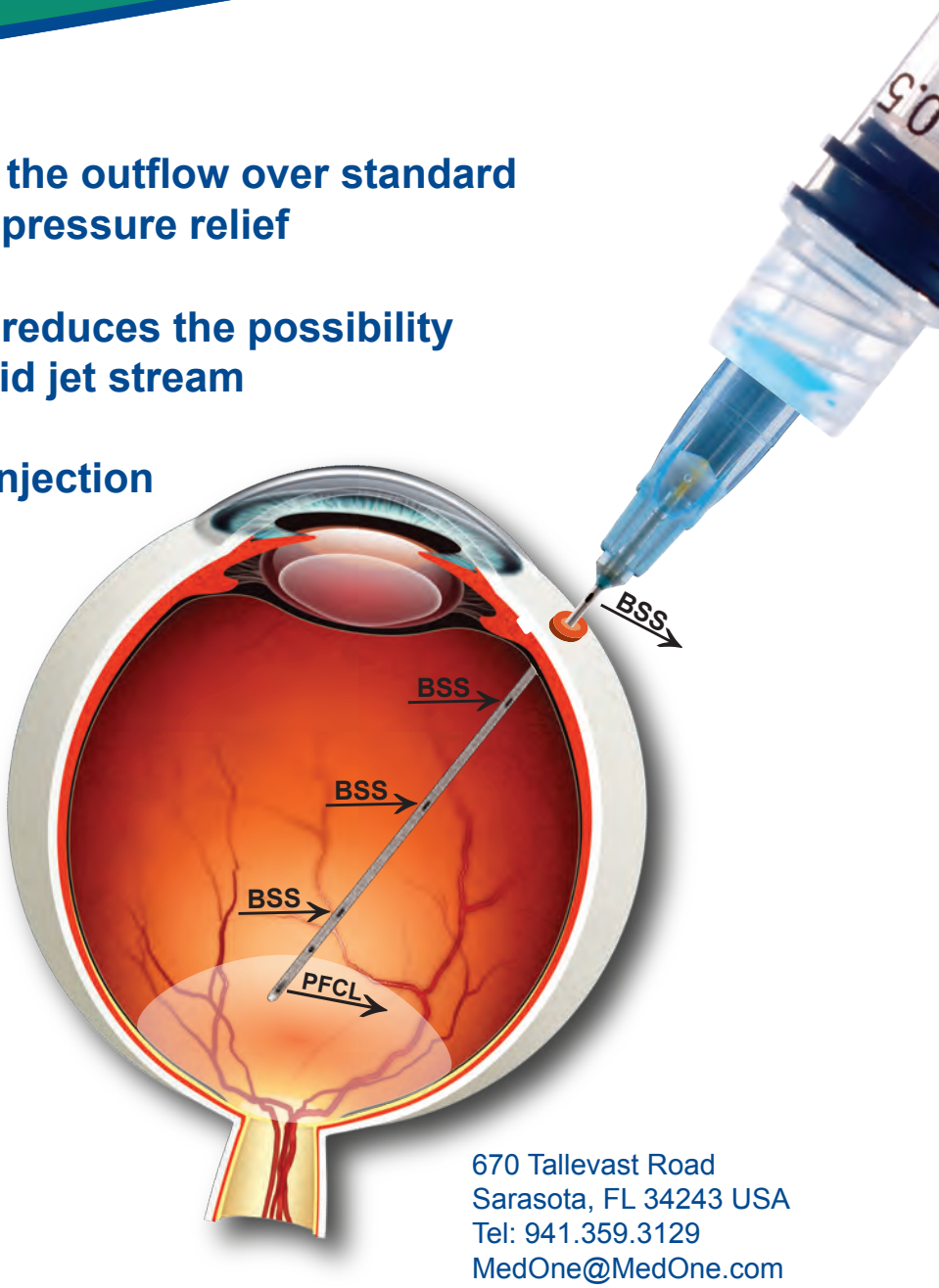

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VBS: A FOCUS ON TRAINEES



Residents and fellows participated in unique programs catered to their specific needs at this year's Vit-Buckle Society meeting.

BY TAVISH NANDA, MD; ROLAKE ALABI, MD, PHD; AND ALEXIS WARREN, MD

"You may be wondering, 'Why the red suit?' Well, that's so bad guys can't see me bleed."

– Deadpool

There were many red super suits at the 11th annual Vit-Buckle Society (VBS) meeting with its superhero theme. For the second year, VBS held a trainee-specific program that addressed early career concerns and stressors, such as contract negotiations, the role of private equity, managing debt, establishing clinical trials, maintaining work-life balance, and even OR neck pain. The morning included sessions for all attendees, while the afternoon added a separate track for the FOstering Careers for Underrepresented Stars (FOCUS) participants. The goal was to help attendees build a protective super suit of their own.

FELLOWS PROGRAM

The Thursday before the main VBS meeting was dedicated to trainees, and it began with a session on "Finance for the Retinal Specialist" led by Sabin Dang, MD, and Jayanth Sridhar, MD. The pair encouraged fellows to "pay the 'future you' first," by setting financial goals early, following a monthly budget, automating a personal allowance, picking a target age for financial independence, and maximizing tax-deferred contributions. Dr. Sridhar urged second-year fellows to allow themselves a single stress-free splurge, post-graduation. "Get it out of your system," he said. "It may be the last time you'll be able to take time off with little to no responsibility."

This segued into a panel discussion during which panelists shared personal stories of their own struggles surrounding mental health and imposter syndrome. Maria Berrocal, MD, and Vivienne S. Hau, MD, PhD, helped to demystify the phenomenon of imposter syndrome, a condition that is not specific to early career physicians but remains a near-constant afterthought. Fellows were encouraged to maintain perspective by sticking to the evidence, focusing on their values, reframing around growth, practicing self-compassion, and seeking feedback from a trusted network.

Trainees then enjoyed a session on "Ergonomics and Physical Wellness" led by Joshua Currie, DPT. Prolonged positioning and stress in the OR, suboptimal posture during slit lamp examinations, and extended procedures using the laser indirect ophthalmoscope are all potential contributors to the increased prevalence of neck and back pain in vitreoretinal surgeons, he said. Dr. Currie encouraged trainees to take preventative measures by using lumbar support chairs and bringing the patient to you at the slit lamp. In addition, he noted that surgeons who engage in regular exercise of any type are less likely to have pain while operating and provided examples of several neck and back strengthening exercises that can reduce the risk of cervical problems and kyphosis.

During the next session on "Leadership in Clinical Trials," Royce Chen, MD, interviewed Tanja Powers, vice president of Ophthalmology Sales and Marketing at Genentech, on her career trajectory and her thoughts on leadership. Ms. Powers described her servant-led style of leadership, which allows her to focus on empowering employees and getting to know them holistically. She shared what she looks for when recruiting physicians for her team: collaborative, patient-centric, and curious individuals who are willing to speak their minds and maintain an open dialogue.

Afterward, esteemed panelists discussed being at the forefront of advanced retina care, including the difficulty in gaining recognition and establishing clinical trials as a solo practitioner. Manuel Amador, MD, shared his industry focus on well-established clinic networks that can provide immediate high-quality imaging and patient volumes. Fellows interested in clinical trials were encouraged to consider practices with an established clinical trials arm.

Next, Dr. Sridhar; Alex L. Ringeisen, MD; and Nika Bagheri, MD, discussed the pros and cons of private practice versus academic career settings. Retina is unique in that most large industry led trials are performed within the private practice setting, they said. While academia can provide a better work-life balance, scheduled administrative time, and teaching opportunities, it can also be marred by red tape, inefficiency, and a pay ceiling. The panel explained that being a private practice partner may offer higher pay and greater efficiency, but it requires a business owner mentality.

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*IQVIA U.S. Medical Claims Data: number of injections administered from Q4 2020 through Q3 2021; Data on file.

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†Data represent payers across the following channels as of November 2022: Medicare Part B, Commercial, Medicare Advantage, and VA. Individual patient coverage is subject to patient's specific plan.

FIND OUT MORE
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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. February 2023. **2.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **3.** Data on file. Regeneron Pharmaceuticals, Inc.

REGENERON®

777 Old Saw Mill River Road, Tarrytown, NY 10591 02/2023 EYL.23.02.0167

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.

5.4 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 (5.4)*]

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 adult 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).

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 adult patients 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 in adult patients 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 have been demonstrated in two clinical studies of pre-term infants with ROP. These two studies randomized pre-term infants between initial treatment with EYLEA or laser. Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment.

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.

10 OVERDOSAGE
Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

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: 02/2023
Initial U.S. Approval: 2011

Based on the February 2023 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.23.02.0006

Figure 1. Basil K. Williams Jr, MD, founder of the FOCUS program, introduced the event's first panel of speakers.

Figure 2. FOCUS participants gathered at the end of the Friday program.

One of the most useful sessions was on contract negotiation, led by Claire Kalia, JD, a contract lawyer with vast experience in the health care sector. She dissected excerpts from real contracts and highlighted verbiage and restrictions that are unfavorable to a naïve applicant. "Ask for nine things, when you only want four," was her sage advice. Even if the salary is inflexible, practices are likely to acquiesce on additional education, paid time off (including parental leave), moving reimbursement, or loan repayment. In some instances, the tax implications can be advantageous for both parties. Ms. Kalia discussed the dangers and enforceability of non-compete clauses and the importance of adding protections against a private equity buyout. She emphasized that the partnership track should also be outlined in every associate contract. Fellows were advised to remember that they are in the driver's seat. "I have never seen an offer pulled because someone asked for more," she explained.

In the final session of the Fellows Program, panelists provided tips and tricks for successfully navigating early career challenges. They urged fellows to lean on their communities and families and to remember that things often balance out over time. Other topics included the tricky reality of how parental leave is handled by different practices, how to build a reputation in the community (give out your cellphone number!), and how to establish an appropriate patient volume. John B. Miller, MD, encouraged fellows to mentally prepare with a detailed plan for surgical cases the night before, and all panelists agreed that it is important to embrace seeing patients with complications, rather than trying to steer clear of your mistakes.

The detail and honesty of the program left a lasting impression on attendees. From personal stories of an unexpected private equity buyout to traumatizing complications in the OR, we learned that not all heroes wear capes. Many wear indirects.

FOCUS PROGRAM

The second half of the day included special programming for the invite-only FOCUS participants. This year, the program included 32 trainees—nine residents, 22 medical students, and one vitreoretinal fellow. The first discussion centered on maximizing mentorship relationships with pointers from some of the best in retina: R.V. Paul Chan, MD, MSc, MBA; Hong-Uyen Hua, MD; Jessica Randolph, MD; and Adrienne W. Scott, MD (Figure 1). Trainees also had an opportunity to learn the top tips and tricks for standing out and navigating meetings from Jordan D. Deaner, MD; Dr. Berrocal; and Dr. Hau. The agenda wrapped up with one of the most moving sessions of the day—a discussion of some of the difficulties and pitfalls we all may experience throughout our training. This conversation, led by Basil K. Williams Jr, MD, and Maria Paula Fernandez, MD, emphasized that our vulnerabilities might prove to be our strongest tools for encouraging and relating to the next generation of ophthalmologists.

Later that evening, the FOCUS participants met and conversed with VBS leadership in a private happy hour (Figure 2). Moving forward, trainees will maintain these connections throughout the year by participating in online "office hours," during which VBS faculty will be available to field questions or concerns. ■

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INTERNATIONAL RETINAL IMAGING SYMPOSIUM

THE LATEST IN IMAGING FROM INTRIS

The 2023 International Retinal Imaging Symposium was a can't-miss event. Here's why.

BY SHILO VOICHANSKI, MD, AND NEDA ABRAHAM, MS

The 2023 International Retinal Imaging Symposium (IntRIS) was held on March 31-April 1, at the Luskin Conference Center in Los Angeles. The 2-day meeting, organized by David Sarraf, MD; Amani A. Fawzi, MD; K. Bailey Freund, MD; and SriniVas R. Sadda, MD, convened in person for the first time since the COVID-19 pandemic. And it was worth the wait. The program was packed with exciting sessions and stimulating talks, delivered by leading experts (Figure), and covered a broad array of topics and the newest innovations in retinal imaging. Here, we share some of the key topics presented.

Figure. This year's International Retinal Imaging Symposium boasted a robust roster of speakers from around the world. Pictured here (left to right) are Gemmy Cheung, MD; Marion R. Munk, MD, PhD; Christine A. Curcio, PhD; Amani A. Fawzi, MD; David Huang, MD, PhD; David Sarraf, MD; Monica Kim; K. Bailey Freund, MD; Richard F. Spaide, MD; Giuseppe Querques, MD, PhD; Michael S. Ip, MD; SriniVas R. Sadda, MD; Barbara Blodi, MD; Seung-Young Yu, MD; and Philip J. Rosenfeld, MD, PhD.

TECHNOLOGY INNOVATIONS

The first day started with lectures that introduced novel imaging systems and promising developments in artificial intelligence. Topics included adaptive optics scanning light ophthalmoscopy, which can enable in vivo microscopy with better photoreceptor identification, according to Richard B. Rosen, MD. David Huang, MD, PhD, discussed split spectrum OCT optoretinography, and Amitha Domalpally, MD, PhD, shared her expertise on artificial intelligence algorithms for the measurement of geographic atrophy (GA). Emanuele Crincoli, MD, FEBO, touched on deep learning for the automatic prediction of early activation of treatment-naïve quiescent macular neovascularization in AMD.

NOVEL RETINAL DISEASES

The meeting made it clear that innovative retinal imaging and advanced technology allow recognition and detection of novel retinal entities. Dr. Freund presented on the distinctive multimodal imaging features of stellate multiform amelanotic choroidopathy, the recognition of which may avoid unnecessary diagnostic testing and interventions. Next, Dr. Sarraf illuminated the audience on the common pathogenetic pathway of vitelliform lesions and introduced the novel entity of pachyvitelliform maculopathy.

UPDATES ON COMMON RETINAL PATHOLOGIES

After the excitement of novel technologies and pathologies, the next few sessions focused on another useful clinical topic: the newest retinal imaging insights into already well-established retinal diseases, such as wet and dry AMD, retinal vascular disease, and myopic degeneration. Christine A. Curcio, PhD, discussed the role of drusen versus subretinal drusenoid deposits in the pathophysiology of AMD and presented new insights into the associated photoreceptor, retinal pigment epithelium, and choroidal changes. Philip J. Rosenfeld, MD, PhD, proposed that the onset and growth of persistent hypertransmission defects detected on en face OCT images of eyes with intermediate AMD can serve as stand-alone primary endpoints in clinical trials designed to test if new therapies slow disease progression.

Speaking of those new therapies, the controversial topic of treating GA with complement inhibition was addressed by Richard F. Spaide, MD, who questioned the need for investigating treatment with no proven functional benefit. He presented a mathematical formula that raised questions about the anatomical benefit as well. This provoked a lively and somewhat heated debate among the participants.

Next, Jeremy A. Lavine, MD, PhD, discussed the cellular

dynamics in diabetic retinopathy (DR). He showed that there is an increase in retinal surface macrophages in advanced forms of DR. Dr. Fawzi then used adaptive optics scanning light ophthalmoscopy to show a loss of pericytes early in the disease course and how protecting these cells may play a role in DR prevention.

A few interesting questions were answered during the conclusion of the day. For example, when asked if GA is better characterized by multicolor imaging or fundus autofluorescence, Dr. Crincoli said that it depends on what we want to evaluate. Foveal sparing is best shown with multicolor imaging, whereas atrophy extension is better evaluated with fundus autofluorescence. And what is PEDCI? Jay Chhablani, MD, explained the origin of pigment epithelial detachment composition indices, which is a novel OCT biomarker to evaluate wet AMD activity that may be integrated with future deep learning models.

ADVANCES IN RETINAL IMAGING

The second day of the meeting began with the fascinating image embossing technique introduced by Dr. Sadda, who showed that applying it to flash color fundus images can enhance detection of subtle abnormalities such as reticular pseudodrusen, even if done retrospectively in historical datasets. Steven D. Schwartz, MD, provided a glimpse into the development of an eccentric OCT adaptive optics system for a high-resolution imaging of the far peripheral retina.

BREAKTHROUGHS

Sessions regarding macular telangiectasia type 2, inherited retinal diseases, central serous chorioretinopathy, and polypoidal choroidal vasculopathy showed how much progress has been made in understanding various retinal diseases. Some of the most memorable talks included one by Paul S. Bernstein, MD, PhD, who presented the results of a multimodal retinal imaging study (including fluorescence lifetime imaging ophthalmoscopy) of adults with Down syndrome who had macular telangiectasia type 2. Anita Agrawal, MD, showed minimal to mild phenotype progression in most patients with peripherin/retinal degeneration slow dystrophy. Gemmy Cheung, MD, presented surprising similarities between wet AMD and polypoidal choroidal vasculopathy in terms of choroidal venous alterations and vascular remodelling. Prithvi Ramtohul, MD, discussed en face ultra-widefield OCT of the vortex vein system in central serous chorioretinopathy, outlining our recent understanding of the venous outflow congestion mechanism of the disease.

THE ANNUAL YANUZZI AWARD LECTURE

The highlight of the second day was the 4th annual Lawrence A. Yannuzzi award lecture. This year, the IntRIS leadership recognized Cynthia A. Toth, MD, who pioneered both the first hand-held spectral-domain OCT system for infant examination and the first intraoperative OCT-guided ophthalmic surgical system with heads-up display. Following a detailed and amusing introduction by Dr. Spaide, Dr. Toth provided a thorough review of the evolution of OCT systems and a beautiful presentation of current and future perspectives that will be essential in extending the boundaries of OCT imaging into the next era of retinal imaging.

MEMBERS-IN-TRAINING PRESENTATIONS

A refreshing addition to the IntRIS meeting this year was the integration of members-in-training as presenters during two special sessions dedicated to the younger generation of retinal imaging researchers. Judging by the audience reactions and the lively discussions and debates that followed, this was the beginning of a wonderful tradition. The sessions were filled with top-notch lectures, covering key topics in retinal imaging innovations, such as: adaptive optics flood illumination imaging; OCT angiographic features of early phase type 3 neovascularization; evaluation of the activity of microaneurysms by combining OCT angiography and OCT images; morphometrics of drusen in AMD and normal aging eyes using OCT; progression of pentosan polysulfate maculopathy; and a memorable glimpse into the future of retinal surgery with a presentation of an intraocular A-scan probe with 1-µm precision.

UNTIL NEXT YEAR

The robust program provided a great platform for learning, discussion, and further research. It showcased the integral role of innovative retinal imaging in the evaluation and management of retinal disease and highlighted the importance of a meeting dedicated solely to retinal imaging. To the organizers, presenters, and participants, one wish remains: repeat the success of this innovative meeting next year in Los Angeles! ■

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THE EYE: A WINDOW TO THE HEART

OCT imaging has helped researchers link retinal changes with the incidence of high-risk vascular diseases.

BY YANG FEI, MD; EMANUEL MORDECHAEV, BA; AND R. THEODORE SMITH, MD, PHD

Researchers have been exploring the association between cardiovascular disease and AMD for decades. Our team at the New York Eye and Ear Infirmary (NYEE) of Mount Sinai recently found that patients with a specific form of AMD with subretinal drusenoid deposits (SDDs) are highly likely to have either underlying heart damage from heart failure and heart attacks, advanced heart valve disease, or carotid artery disease associated with certain types of strokes.[1,2]

This research is the first to identify which types of high-risk vascular diseases (HRVDs) are linked to the presence of SDDs.[1] The findings could prompt increased screening to save vision, help diagnose undetected heart disease, and prevent adverse events. New approaches to proper multidisciplinary screening of these chronic diseases in at-risk populations may serve to greatly reduce morbidity and mortality.

THE STUDY

Our study of 200 patients with intermediate AMD found that 85% of those with a history of myocardial infarction, heart failure, major valve disease, and/or ischemic stroke had SDDs on multimodal imaging. We found that AMD patients with these cardiovascular diseases and stroke were nine times more likely to have SDDs than those without them.[1]

The study suggests that SDDs are markers for a retinal disease that is distinct from soft drusen and may be driven by systemic vascular disease. Therefore, patients with SDDs (with or without soft drusen) may require more than the standard vitamin supplementation; they may need a trip to the cardiologist or neurologist for evaluation of underlying disease (Figure 1). A standard cardiovascular workup with a transthoracic echocardiogram (TTE) and computed tomography angiography (CTA) could save the patient from a life-threatening event.

UNDERSTANDING THE PARADIGM

The retina, especially its photoreceptors, consumes oxygen more rapidly than any other tissue in the human body. This photoreceptor layer is where SDDs are found, and its blood supply from the choroid may give a clue to the pathophysiology. The choroid is an end-arterial system (without adjacent anastomosis) that provides the greatest blood flow per unit mass and, unlike the retinal circulation, does not derive protection by autoregulation. Thus, the literature has confirmed generalized choroidal thinning in the setting of coronary artery disease (CAD).

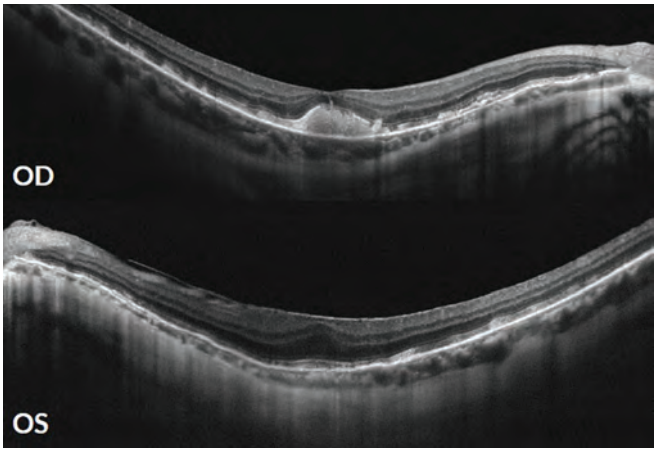

Figure 1. SD-OCT of a 55-year-old patient with intermediate AMD reveals bilateral SDDs with few soft drusen. Subfoveal choroidal thickness was reduced at 159 µm OD and 99 µm OS. A pseudovitelliform macular lesion is also noted in the right eye. Subsequent cardiovascular and neurovascular workup revealed 40% internal carotid stenosis bilaterally.

In another study conducted at NYEE, 38 subjects with CAD and no known retinal disease were imaged with near-infrared reflectance and spectral-domain (SD) OCT for the presence of SDDs.[3] SDDs were significantly more frequent (relative risk = 2.1) in subjects with CAD versus those without, with no association seen between CAD and soft drusen.

We hypothesized a straightforward vascular mechanism for the association: The blood supply to the eye is directly diminished by these diseases, either by heart damage that diminishes systemic blood supply or from a blocked carotid artery that directly impedes blood flow to the eye. A poor blood supply can cause damage to any part of the

body, which manifests as SDDs in the retina. We concluded that SDDs are the result of when an already under-supported choroidal perfusion cannot compensate for a reduction in arterial blood supply (eg, CAD or other HRVDs).[3]

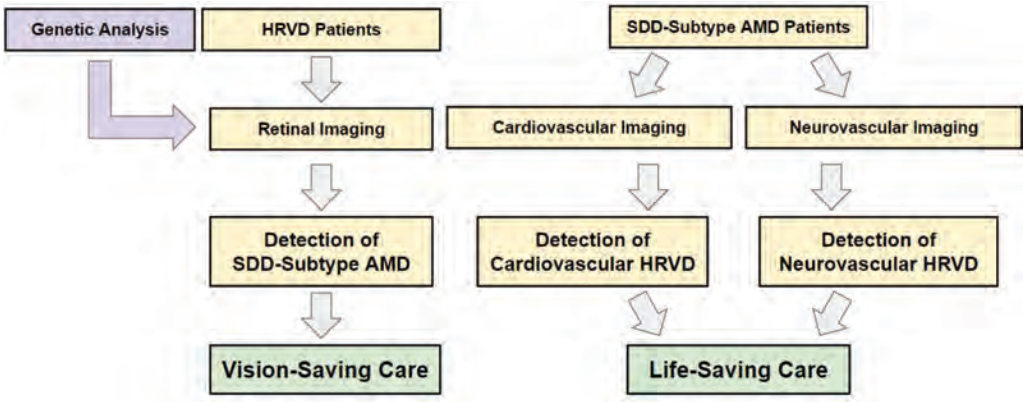

Figure 2. This diagram shows the pathways by which a singular diagnosis can lead to multidisciplinary care. Genetic workup, specifically for homozygous *ARMS2* mutation, is another way to identify an at-risk population for SDD-subtype AMD.[6]

A CLOSER LOOK

We investigated further and recruited 86 patients from the inpatient stroke and cardiac units at Mount Sinai Hospital for a cross-sectional study. We found that SDDs, as imaged by SD-OCT, are present in 26% (8/31) of stroke patients and 33% (18/55) of cardiac patients.[4] This initial finding confirms the Alabama Study of Early Age-Related Macular Degeneration (ALSTAR) finding of SDDs in approximately 25% of older adults.[5] SDDs are strongly associated with AMD severity and progression. In the same ALSTAR study, SDDs were present in 49% of early AMD and 79% of intermediate AMD patients.

Findings from the same preliminary data of 86 inpatients corroborate the association between HRVD and SDDs. SDDs showed a significant correlation with both internal carotid artery stenosis by CTA and cardiac index calculated from TTE. Thus, SDDs may be the lynchpin that connects ophthalmology, cardiology, and neurology when caring for these patients (Figure 2).

FUTURE PLANS

While this data suggest the utility of screening for SDDs in at-risk patient populations, the relationship between AMD and vascular disease has never been fully evaluated. The exact parameters and cutoff needed for adequate noninvasive and cost-effective screening remain under investigation. We continue to question whether SD-OCT is the best imaging modality for SDD detection. While it has frequently been used as the standard for evaluating AMD, SD-OCT image capture and analysis require trained individuals.

We partnered with iHealthScreen to develop automated artificial intelligence (AI)-based AMD screening and prediction tools based on color fundus photographs.[7] An embossed photo technique—in which each pixel was replaced by a highlight or a shadow depending on light and dark boundaries present in the original fundus photographs—showed a high sensitivity for detecting SDDs compared with multimodal image analysis.[8] Preliminary data on 1,115 color fundus photographs obtained for the AI-based AMD screening compared with SD-OCT showed > 90% positive and negative predictive values.[9] Through this new embossed photo technique, screening for SDD in clinical practice could become AI-automated.[9]

We now know that SDDs are strongly associated with vascular disorders, and they may one day be widely recognized as a biomarker of cardiovascular and neurovascular compromise, allowing for effective referral to specialists and prevention of death and blindness. ■

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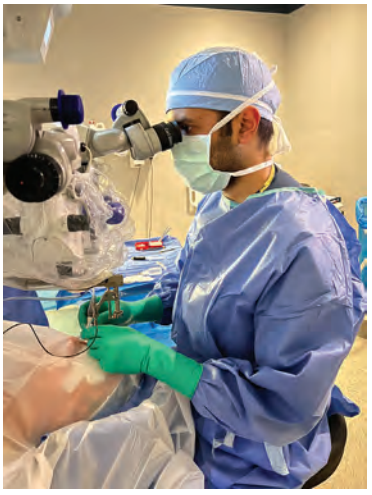
WHERE IT ALL BEGAN

Ananth Sastry, MD, grew up in Tampa, Florida, with his younger sister. They were fortunate to be raised by loving and supportive parents who encouraged them to pursue their dreams. In grade school, Dr. Sastry had a wide range of interests, which included science, literature, philosophy, music, chess, and martial arts. However, his love for science ultimately prevailed and led him to medicine.



Dr. Sastry's Advice:
Continue to grow, learn, and evolve even after fellowship. Discuss cases with colleagues and attend meetings to get varying perspectives. Keep an open mind and try new ideas, techniques, and technology.

HIS PATH TO RETINA

As an undergraduate studying ophthalmic immunohistochemistry in the lab of Jeffrey Goldberg, MD, PhD, Dr. Sastry became fascinated by the structure and function of the retina and how each layer plays a role in visual physiology. This interest was nurtured in medical school, when he witnessed the elegance of retinal surgery during his ophthalmology rotation.

His love for retina was solidified in residency through his interactions with Mark Humayun, MD, PhD. His inventive work, which fused engineering and medicine to create the Argus II retinal prosthetic (Second Sight Medical Products), inspired Dr. Sastry to pursue a career in retina and fostered his interest in innovation.

SUPPORT ALONG THE WAY

Dr. Sastry's parents are his most important mentors and guiding lights. His father, a cardiothoracic surgeon, taught him the virtues of hard work, discipline, persistence, and integrity. His mother, a small business owner, instilled in him the values of compassion, empathy, and sincerity.

In college and medical school, Dr. Goldberg introduced him to ophthalmology through basic science and imbued in him a deep love of scientific inquiry. Anat Galor, MD, and Chrisfouad Alabiad, MD, were also instrumental in Dr. Sastry's path to pursuing an ophthalmology residency.

In residency, Vivek Patel, MD, showed him how an exemplary physician can grow through the constant pursuit of mastery in one's field. Damien Rodger, MD, PhD, and Narsing Rao, MD, were both very supportive of Dr. Sastry's pursuit of a surgical retina fellowship and inspired his interest in uveitis.

In fellowship, Sharon Fekrat, MD; Cynthia A. Toth, MD; and Lejla Vajzovic, MD, helped Dr. Sastry grow tremendously as a surgeon and aspiring clinician-scientist. Their support in his career development has been invaluable.

AN EXPERIENCE TO REMEMBER

Dr. Sastry recently cared for an artist who had severe diabetic retinopathy and had lost vision in each eye, one of which had a complex tractional retinal detachment. Due to her disability, she was no longer able to create and sell her art, which was her livelihood. After undergoing bilateral surgery, she recovered her vision and was able to paint again. At her last follow-up visit with Dr. Sastry, she informed him that she had sold out her latest art show and gifted him with a beautiful painting that she had made after recovering from her surgery. ■

Ananth Sastry, MD, is an attending surgeon and faculty member of the Vitreoretinal Service at the Cleveland Clinic Cole Eye Institute. He spends 80% of his time seeing patients, performing surgery, and teaching trainees and the remaining 20% on research. His clinical practice primarily focuses on medical and surgical retina, and he also manages uveitis patients. Dr. Sastry is a consultant for Allergan/Abbvie and is on the advisory board for Apellis Pharmaceuticals and Genentech/Roche. He can be reached at **ananth.sastry@gmail.com**.

SURGICAL DRAINAGE OF LARGE MACULAR CYSTS IN COATS DISEASE


Consider this approach in cases of retinal edema after ineffective laser or pharmacologic therapies.

BY RODNEY FONG, MS, AND GLENN YIU, MD, PHD

Coats disease, a retinal vascular condition, is typically marked by unilateral retinal telangiectasias and abnormal microaneurysm formation without any known systemic disease.[1,2] The management goals generally aim to preserve vision by limiting or eliminating telangiectatic vessels, leaking aneurysms, and subretinal exudates. However, advanced or refractory cases often result in poor outcomes.[3] Peripheral lesions can often be managed with laser photocoagulation or retinal cryopexy, whereas macular pathology often requires laser treatments and intravitreal pharmacotherapies, such as anti-VEGF agents or steroids.[2,4,5]

Recently, we encountered a young man with Coats disease who exhibited very large macular cysts and dense subretinal exudates that were previously refractory to both laser and intraocular injections. We decided to attempt surgical drainage of the retinal cysts.

THE CASE

A 30-year-old man with Coats disease in his left eye presented with worsening vision over several years. Diagnosed at age 9, he received multiple rounds of laser photocoagulation to the peripheral lesions. However, as a young adult, he began to develop macular cysts and exudates that were unsuccessfully managed, which led to his evaluation in our clinic.

At presentation, his VA was 20/400 in the affected eye with large macular cysts seen on fundus examination (Figure 1A). The cysts were located mostly in the

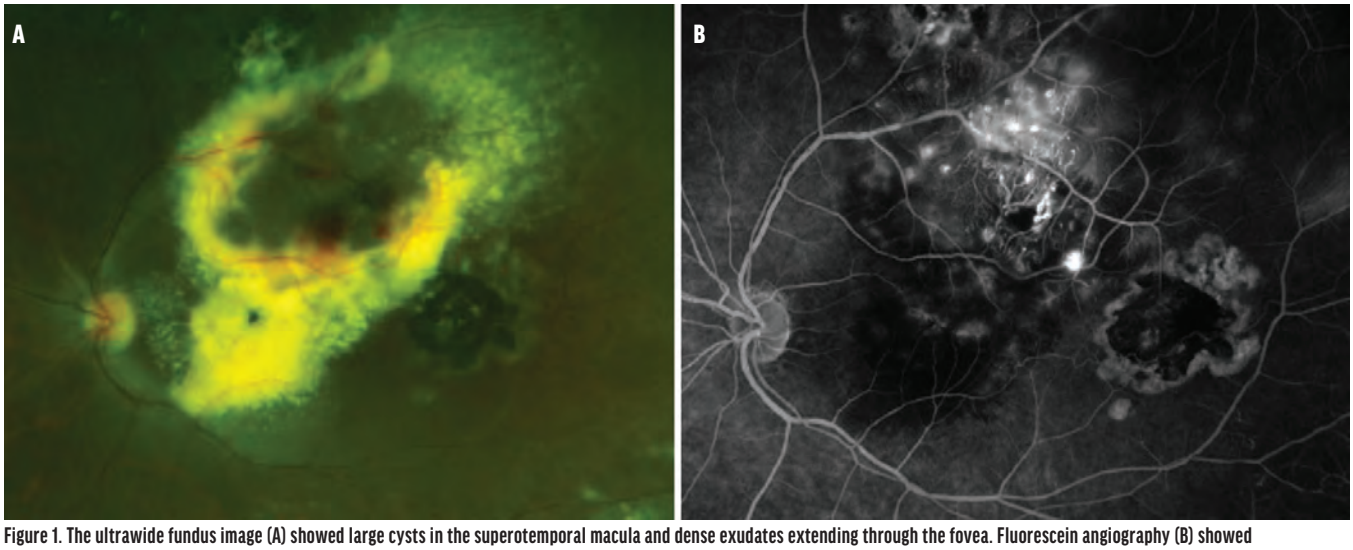


Figure 1. The ultrawide fundus image (A) showed large cysts in the superotemporal macula and dense exudates extending through the fovea. Fluorescein angiography (B) showed telangiectasias and large microaneurysms associated with the large cysts, as well as laser photocoagulation scars in the temporal macula from previous treatment.

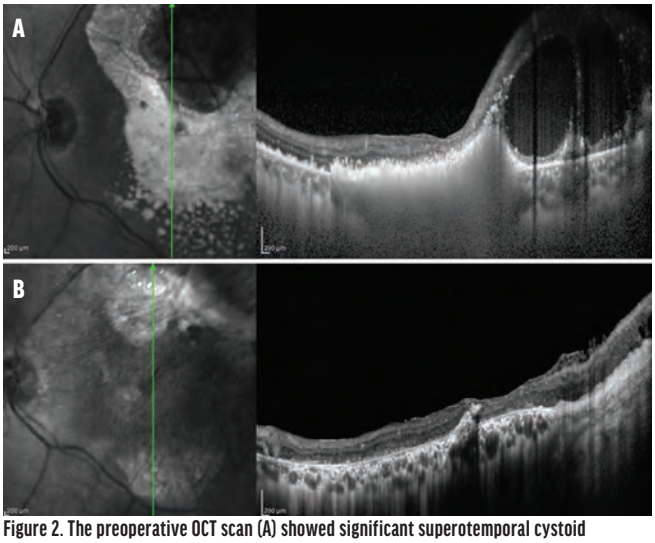


Figure 2. The preoperative OCT scan (A) showed significant superotemporal cystoid macular edema and large exudates, and the postoperative OCT scan (B) showed resolution of fluid and exudates.

superotemporal macula and accompanied by retinal telangiectasias and light-bulb aneurysms, which leaked on fluorescein angiography (Figure 1B). Dense subretinal exudates extending through the fovea were seen on OCT imaging (Figure 2A), which accounted for the severity of his vision loss.

We began treatment with additional photocoagulation and multiple rounds of anti-VEGF therapy, but the intraretinal fluid did not abate. The vascular lesions showed no laser uptake despite increasing the energy and duration of the laser, likely due to the thick layer of retinal fluid insulating the retinal vasculature from the laser's energy uptake at the level of the retinal pigment epithelium. His macular edema worsened despite aggressive treatment.

After extensive discussion about the risks, benefits, and alternatives, we decided to pursue pars plana vitrectomy with surgical drainage of the intraretinal cysts and laser photocoagulation.

THE SURGICAL DRAINAGE

Using 23-gauge instrumentation, we performed a standard three-port pars plana vitrectomy. Initially, we intended to use a 41-gauge subretinal cannula to perform the drainage with intraoperative OCT guidance. However, the tip of the 41-gauge cannula was clogged by the thick, viscous contents of the chronic cysts, preventing us from effectively aspirating the fluid. We switched to endodiathermy, and created a small retinotomy that allowed for aspiration using a 25-gauge soft-tip cannula. After fluid-air exchange, we aspirated the large macular cysts, with visible extrusion of the yellowish exudates through the retinotomy. This enabled us to perform endolaser to ablate the aneurysms and vascular lesions.

We left the patient with 25% SF_6 gas and noted no residual fluid at the 1-month postoperative visit. Over the subsequent year, the exudates gradually receded (Figure 2B), although his VA was 20/200.

THE RESULTS

Our case demonstrates a proof of concept of the possibility of surgically draining large macular cysts in cases that are refractory to standard laser photocoagulation or intravitreal therapies. Although the patient did not regain most of his vision, we attributed this to the prolonged duration of the subretinal exudates that were inadequately treated, resulting in photoreceptor degeneration and loss of the outer retinal layers, as seen on the postoperative OCT scans. Had he undergone surgical management at an earlier time, more of his vision might have been recovered, evidenced by the rapid resolution of the retinal fluid and dense exudates.

Generally, we believe that surgical intervention, especially in a young patient with a formed vitreous, should be left as a last-resort intervention. However, this case suggests that surgically draining large retinal cysts could be considered in select cases of retinal edema for which laser or pharmacologic therapies are ineffective.

Our experience also taught us that chronic intraretinal fluid, as with subretinal fluid in longstanding retinal detachments, can be challenging to remove and requires the use of a drainage retinotomy. We chose a slightly more expansile concentration of a short-acting gas to tamponade and compress the retinal tissue, although the effectiveness of such an approach is unclear.

We hope that sharing this unique case of surgically draining macular cysts in a patient with Coats disease helps to guide other vitreoretinal surgeons who are considering this approach in clinically appropriate cases. ■

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MASTERING PRACTICE EFFICIENCY AND FLOW

Insights on managing patient flow, minimizing distractions, and balancing efficiency with patient-doctor relationships.

BY ABTIN SHAHLAEE, MD, AND OMESH GUPTA, MD, MBA

There are some days when everything goes well, but then there are days when everything seems to go wrong, and you find yourself falling behind schedule by 1 or 2 hours. By the end of the day, you may be wondering whether the wrong turn was due to your actions or staffing issues.

Running a medical practice requires more than just providing quality care to your patients. It also involves ensuring that your office runs smoothly and efficiently, which allows you to provide the best possible care to your patients while also maximizing productivity and profitability.

In this article, Omesh Gupta, MD, MBA, shares his insights on the most effective ways to streamline office operations, optimize patient flow, and manage staff for maximum efficiency.

ABTIN SHAHLAEE, MD: WHAT IS YOUR GENERAL WORKFLOW ON A GIVEN CLINIC DAY?

Dr. Gupta: My schedule is fairly unstructured in terms of new patients, established patients, and injection slots. There are sometimes variations in the overall format depending on the office location. For example, some offices can handle higher volumes, while other offices have lower volumes to accommodate for last-minute patients or teaching.

The unstructured schedule template improves the scheduling efficiency and flexibility for the call center as well as the front desk. The more restrictions in your schedule, the more time it takes to find an open spot. This is a common issue at the front desk on busy office days. Another reason I keep my schedule unstructured is due to the efficiency of my offices. The staff works well as a team, and each member has a designated function that allows the team to handle any patient that has an appointment.

DR. SHAHLAEE: WHAT ARE THE THREE MOST COMMON MISTAKES THAT YOU SEE MADE IN TERMS OF THE INEFFICIENCY IN PATIENT FLOW?

Dr. Gupta: The biggest issue that affects efficiency is doctor distractions. Inevitably, physicians are pulled in many different directions. Personal phone calls, informal meetings, and responding to nonurgent emails can throw you off schedule. I try to limit these types of distractions almost to the point of eliminating them completely during clinic hours. You should not be interrupted when you are seeing patients. These distractions can occur frequently throughout the day, and each occurrence takes valuable time away from your patients.

Another common issue is seeing patients late from the start. It is easy to fall behind with unexpected issues, especially on busy days. However, if you are starting the day late, it is going to be a challenge to get back on time and then stay on time for the rest of the day.

Lastly, the responsibility of running an efficient office does not fall on one person, and the culprit for an inefficient office is usually not only one issue. It is crucial to recognize that running an efficient office requires a team effort and a multifactorial solution.

THE CULPRIT FOR AN INEFFICIENT OFFICE IS USUALLY NOT ONLY ONE ISSUE. IT IS CRUCIAL TO RECOGNIZE THAT RUNNING AN EFFICIENT OFFICE REQUIRES A TEAM EFFORT AND A MULTIFACTORIAL SOLUTION.

DR. SHAHLAEE: WHERE IS THE MOST COMMON BOTTLENECK IN THE OFFICE?

Dr. Gupta: Often, managing lunch breaks and simultaneously ensuring that the floor is covered can be a challenge in many offices. In my opinion, the unhealthy solution is to take a shorter lunch break or to not take a break at all.

This is detrimental in two ways. First, from a nutritional standpoint, staff members and doctors should each have a chance to eat. Second, but equally important, everyone needs a mental and physical break from the clinic flow. Lunch breaks also provide a chance for staff to connect with each other about their life outside of work. It makes the day-to-day busy office volume more sustainable and enjoyable.

Building a lunch break into the template is essential. It allows the office to finish the morning workload before the afternoon patients arrive. The lower volume of patients during this time allows for staff to take a lunch break either simultaneously or stagged, depending on the volume of patients at that time.

DR. SHAHLAEE: HOW HAS TECHNOLOGY AFFECTED PRACTICE EFFICIENCY?

Dr. Gupta: Technology has definitely helped my efficiency. We converted to electronic health records (EHR) many years ago, and patient care is much easier since the conversion—a fact that I do not take for granted. I have much more useful information at my fingertips, and documentation has been dramatically improved. In addition, the front-office and back-office functions have advanced, making it much easier to navigate the increasingly complex world of health care insurance.

However, when converting from paper to EHR, there was definitely some transition cost. We down-scheduled patients to accommodate for loading the patient's information into the EHR. We also converted to the EHR over an extended period of time to minimize patient down-scheduling.

DR. SHAHLAEE: WHAT ARE SOME TIPS FOR KEEPING THE PATIENT-DOCTOR RELATIONSHIP BUT MAINTAINING EFFICIENCY?

Dr. Gupta: This is an excellent question that I think is often overlooked. I intentionally and purposefully greet every patient without looking at a screen or piece of paper. Then, after looking at the chart, examining the patient, and going through imaging, I make another concerted effort to have an unobstructed interaction with the patient before leaving. I answer any remaining questions with as much eye contact as possible.

DR. SHAHLAEE: ANY FINAL PEARLS OR TIPS?

Dr. Gupta: Becoming more efficient takes experience and develops over time. As I say to fellows all the time, "Value patient care over speed. Speed will come with time in the office and the OR." Put patient care first, and the rest will fall into place. Those that place a priority on speed often make mistakes or eventually regret their misdirected priorities.

In today's health care landscape, the efficiency of you and your office is crucial for the successful practice of medicine. It is important to take the time to identify any scheduling and efficiency challenges that your practice may be facing and then implement the necessary changes to address them. By doing so, you can ensure that your practice remains financially successful and on track to provide quality care to your patients. ■

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THE LATEST IN GENE THERAPY CLINICAL TRIALS FOR IRD

Many investigational drugs for inherited retinal disease have made it to phase 2; a few are even in phase 3.

BY LUCIANO C. GREIG, MD, PHD, AND HOSSEIN AMERI, MD, PHD, FRCSI, MRCOPHTH

The number of clinical trials aiming to preserve or restore vision for patients with an inherited retinal disease (IRD) has exploded in recent years.[1] Identification of disease-causing gene mutations is now part of routine clinical care, thanks to the low cost and widespread availability of gene panel testing. As more therapeutic interventions are developed, treatment opportunities should be included in our standard approach to the care of patients with an IRD.

In this article, we highlight some of the latest ongoing phase 2 and 3 gene therapy trials to help retina specialists provide their patients with every available option (Table).

RETINITIS PIGMENTOSA

Botaretigene sparoparvovec (MGT009 [formerly AAV-RPGR], MeiraGTx/Janssen) targets loss of function mutations in the *retinitis pigmentosa (RP) GTPase regulator* (*RPGR*) gene. The gene therapy relies on a stable deletion mutant of the *RPGR* isoform that is missing 126 amino acids but is sufficient to rescue the *RPGR* gene function.[2] Expression is driven by the human rhodopsin (RHO) kinase promoter, and it is packaged into the adeno-associated viral (AAV) 2/5 vector serotype.

A phase 1/2 trial (NCT03252847) compared subretinal injection of low, intermediate, and high doses in patients with X-linked RP (XLRP).[3] The overall safety profile was favorable, and patients in the low- and intermediate-dose cohorts demonstrated improved retinal sensitivity and functional vision at 1 year. Patients receiving the high dose had a decrease in retinal sensitivity, and two of the three patients had inflammatory responses that were steroid responsive. The phase 3 LUMEOS (NCT04671433) trial is currently underway and actively recruiting to enroll 96 patients.

Laruparetigene zosaparvovec (AGTC-501, Beacon Therapeutics) also aims to restore *RPGR* gene function in patients with XLRP and consists of a cone-specific PR1.7 promoter driving expression of a codon-optimized human *RPGR* coding sequence. It is packaged in an AAV2 capsid containing three tyrosine-to-phenylalanine mutations that improve transduction efficiency.[4] The phase 1/2 SKYLINE study (NCT03316560) included 29 patients with XLRP who received one subretinal injection, with the first nine treated in the periphery to test for safety and the subsequent patients treated centrally.[5] The microperimetry sensitivity improved at 1 year in all centrally dosed patients. A phase 2/3 study, VISTA (NCT04850118), is planned with randomization to low- or high-dose AGTC-501 or untreated control with an estimated enrollment of 63 patients.

Cotoretigene toliparvovec (BIIB112, Biogen) is designed to rescue *RPGR* gene function using an RHO kinase promoter to drive full-length human codon-optimized *RPGR* expression. Viral particles are generated using AAV8 capsids and delivered by subretinal injection. A phase 1/2 dose-escalation study, XIRIUS (NCT03116113), did not meet the primary endpoint of ≥ 7 dB improvement from baseline at five or more central microperimetry points at 1 year.[6] However, positive trends were observed across several secondary endpoints, including low luminance visual acuity. Patients

AT A GLANCE

- Several therapies for X-linked retinitis pigmentosa are in phase 2/3 or phase 3 trials, including MGT009 (MeiraGTx/Janssen), cotoretigene toliparvovec (BIIB112, Biogen), and laruparetigene zosaparvovec (AGTC-501, Beacon Therapeutics).
- The phase 2/3 trial of QR-421a (ProQR Therapeutics) for the treatment of patients with Usher syndrome with advanced vision loss is active but not recruiting.
- Optogenetic approaches can be used to make bipolar or retinal ganglion cells sensitive to light, bypassing the need for functional photoreceptor cells.

exiting the trial have been offered enrollment in a separate phase 3 trial, SOLSTICE (NCT03584165), that will monitor long-term outcomes over a 5-year period.

4D-125 (4D Molecular Therapeutics) is in a phase 1/2 trial, EXCEL (NCT04517149), for the treatment of patients with XLRP. This gene therapy uses a proprietary AAV capsid variant developed by the company, R100, to deliver a functional copy of the *RPGR* gene to the photoreceptors. In phase 1, patients were treated with one of two doses: 3E11 vg/eye or 1E12 vg/eye; in the phase 2 expansion portion, patients are treated with the latter dose. The therapy received FDA fast track designation, and the trial is active.[7]

TABLE. GENE THERAPY TRIALS FOR INHERITED RETINAL DISEASES

Gene	Mutation	Treatment (Sponsor)	Pharmacologic Agent	Mechanism	Delivery	Trial ID	Phase	Primary Completion
Leber Congenital Amaurosis								
GUCY2D	Loss of function	ATSN-101 (Atsena Therapeutics)	AAV8-GRK1-GUCY2D	Restores functional protein	Subretinal	NCT03920007	1/2	May 2023
CEP290	c.2991+1655A>G	AGN-151587 (Allergan)	AAV5-GRK1-Cas9	Genome editing	Subretinal	NCT03872479 (BRILLIANCE)	1/2	May 2025
		EDIT-101 (Allergan/Editas)	EDIT-101	Eliminates mutation		NCT03872479		
Choroideremia								
CHM	Loss of function	4D-110 (4D Molecular Therapeutics)	AAV.R100-hcoREP1	Restores functional protein	Subretinal	NCT04483440 (CHORUS)	1/2	June 2024
X-Linked Retinitis Pigmentosa (RP)								
RPGR	Loss of function	Botaretigene sparoparvovec (MeiraGTx/Janssen)	AAV5-RhoK-RGPRdel	Restores functional protein	Subretinal	NCT04671433 (LUMEOS)	3	March 2024
		Laruparetigene zosaparvovec (Beacon Therapeutics)	rAAV2tYF-GRK1-RPGR			NCT04850118 (VISTA)	2/3	January 2024
		4D-125 (4D Molecular Therapeutics)	AAV.R100-hcoRGPR			NCT04517149 (EXCEL)	1/2	June 2026
		BIIB112 (Biogen)	AAV8-RPGR			NCT03584165 (SOLSTICE)	3	June 2026
RP								
RHO	P23H	QR-1123 (ProQR Therapeutics)	antisense oligo	RNaseH mediated degradation	Intravitreal	NCT04123626 (AURORA)	1/2	June 2022
PDE6b	Loss of function	CTx-PDE6b (Coave Therapeutics)	AAV2/5-hPDE6B	Restores functional protein	Subretinal	NCT03328130	1/2	January 2023
Leber Hereditary Optic Neuropathy								
NADH dehydrogenase	G11778A ND4	GS010 (Gensight Biologics)	rAAV2/2-ND4	Restores functional protein	Intravitreal	NCT03293524	3	June 2024
Usher Syndrome								
USH2A	Exon 13	QR-421a (ProQR Therapeutics)	antisense oligo	Induces exon skipping	Intravitreal	NCT05158296 (SIRIUS)	2/3	August 2022
Optogenetics								
Non-genotype specific (RP patients for trial)		BS01 (Bionic Sight)	AAV2-CAG-ChronosFP	RGC stimulus w/ headset pattern transformation	Intravitreal	NCT04278131	1/2	December 2024
		Sonpiretigene isteparvovec (Nanoscope Therapeutics)	AAV2-mGluR6-MCO1	Direct bipolar cell stimulation		NCT04945772 (RESTORE)	2	March 2023
		GS030 (Gensight Biologics)	rAAV2.7m8-CAG-ChrimsonR-tdTomato			NCT03326336 (PIONEER)	1/2	December 2022
Non-genotype specific (Stargardt patients for trial)		Sonpiretigene isteparvovec (Nanoscope Therapeutics)	AAV2-mGluR6-MCO1			NCT05417126 (STARLIGHT)	2	July 2023

AAV2/5-hPDE6B (CTx-PDE6b, Coave Therapeutics) is designed to deliver a functional copy of the *PDE6b* gene to the subretinal space to induce transgene expression and synthesis of functional PDE6b proteins in photoreceptive rods and cones. The ongoing phase 1/2 trial (NCT03328130) has enrolled 17 patients with *PDE6b*-associated RP randomly assigned to one of four dosing cohorts. The preliminary 12-month data suggest the drug is well tolerated, and a subgroup of six patients with early disease treated with the high dose experienced positive efficacy; based on microperimetry, the patients showed improved retinal sensitivity in treated eyes compared with untreated eyes.[8]

QR-1123 (ProQR Therapeutics) is an antisense oligonucleotide that reduces the expression of the P23H protein selectively while preserving the expression of the wild-type RHO protein. The phase 1/2 trial (NCT04123626) includes up to eight single doses and a repeat dose cohort in a total of 11 patients with autosomal dominant RP. Treated patients will be followed for 12 months to evaluate safety, tolerability, and efficacy. The trial is active but not recruiting.

LEBER CONGENITAL AMAUROSIS

SAR439483 (ATSN-101, Atsena Therapeutics) is a gene therapy under investigation in a phase 1/2 dose escalation study for the treatment of *GUCY2D*-associated Leber congenital amaurosis (LCA) 1. Preliminary 6-month data, presented at the 2023 Association for Research in Vision and Ophthalmology meeting, showed that the nine patients who received the high dose had a mean change in retinal sensitivity from baseline that was significantly higher than the change noted in untreated eyes at day 28 and beyond. Two of those high-dose patients demonstrated an improvement in corrected visual acuity greater than 0.3 logMAR (no treated eyes had a decrease in BCVA).[9]

EDIT-101 (AGN-151587, Allergan/Editas) targets the heterozygous or homozygous mutation involving c.2991+1655A>G in intron 26 in the *CEP290* gene implicated in LCA10. The phase 1/2 trial (NCT03872479) is investigating a single subretinal injection of one of five doses in patients with LCA10. The trial is fully enrolled with 34 patients.

USHER SYNDROME

QR-421a (ProQR Therapeutics) is intended to treat patients with Usher syndrome and nonsyndromic RP due to mutations in exon 13 of the *USH2A* gene.[10] A phase 1/2 trial, STELLAR (NCT05176717), enrolled 20 patients who received intravitreal injections of one of three dose levels.[11]

No serious adverse events or ocular inflammation were reported, although one patient had worsening of preexisting cystoid macular edema. Efficacy endpoints demonstrated improved visual acuity with a mean benefit of 6 letters at 6 months after a single injection and total retinal sensitivity improvement of up to 40 dB. The phase 2/3 SIRIUS trial (NCT05158296) for patients with advanced vision loss (baseline VA < 20/40) includes administration of QR-421a at baseline, 3 months, and every 6 months thereafter with 18 months of follow-up.

X-LINKED RETINOSCHISIS

Atsena Therapeutics recently received FDA clearance for its investigational new drug application for a phase 1/2 trial of **ATSN-201** for the treatment of X-linked retinoschisis. The gene therapy uses an AAV.SPR capsid to deliver *RS1* to photoreceptors in the central retina/fovea. The open-label, dose-escalation trial is evaluating the subretinal injection of ATSN-201 in male patients with X-linked retinoschisis caused by pathogenic or likely pathogenic mutations in *RS1*.[12]

LEBER HEREDITARY OPTIC NEUROPATHY

Lenadogene nolparvovec (Lumevoq, GenSight Biologics) uses a mitochondrial targeting sequence to allow for proper expression of a missing or mutated mitochondrial gene—*NADH dehydrogenase*, in the case of study patients with Leber hereditary optic neuropathy.[13]

The company released favorable topline data from its phase 3 REFLECT trial (NCT03293524) 3 years post-treatment. Of the patients who received bilateral intravitreal injections of the study drug, 73% experienced a clinically meaningful improvement of at least -0.3 LogMAR (+15 ETDRS letters) relative to their observed nadir (worst BCVA recorded from baseline).[13] The treatment was well tolerated with the main ocular adverse event being intraocular inflammation that was responsive to treatment.[14]

CHOROIDEREMIA

4D-110 (4D Molecular Therapeutics) is currently under investigation in a phase 1/2 trial (NCT04483440) for the treatment of patients with choroideremia related to mutations in the *CHM* gene. The therapy uses the intravitreal R100 vector to deliver the product to the retina, in the hopes that it will lead to transgene expression in all retinal layers and regions after a single dose. The trial is fully enrolled with 13 patients and is expecting preliminary data in June 2024.[15]

OPTOGENETIC APPROACHES

Optogenetics is the use of exogenous photosensitive proteins (opsins) to enable rapid and precise manipulation of neuronal activity in response to light stimulation.[16] Optogenetic approaches can be used to make bipolar or retinal ganglion cells sensitive to light, bypassing the need for functional photoreceptor cells. Thus, any IRD that causes photoreceptor death or dysfunction while sparing other retinal neurons should theoretically respond to this therapeutic strategy. Several companies have started clinical trials to determine if opsins can restore some level of vision in patients with advanced RP and Stargardt disease.

Sonpiretigene isteparvovec (MCO-010, Nanoscope Therapeutics) targets opsin expression to bipolar cells. It relies on the mGluR6 promoter-enhancer, which is active in ON bipolar cells, to drive expression of multi-characteristic opsin. This therapy is designed to be sufficiently active at ambient light levels, so that no specialized hardware is required to project images to the retina.[17] A phase 1/2 clinical trial (NCT04919473) recruited 12 participants with advanced RP and demonstrated safety of a single intravitreal injection of sonpiretigene isteparvovec.[18] Nine of 11 patients demonstrated 2 luminance level improvements in vision-guided mobility or a 0.3 logMAR gain in visual acuity. A separate phase 2 trial, RESTORE (NCT04945772), demonstrated similar improvements. Vision-guided mobility, shape discrimination, and visual acuity gains were evident in 14 of 18 treated patients compared with three of nine patients receiving a placebo. Another phase 2 trial, STARLIGHT (NCT05417126), is investigating the efficacy of sonpiretigene isteparvovec for Stargardt disease.

GS030 (Gensight Biologics) combines an AAV2-based gene therapy with the use of light-stimulating goggles for the treatment of end-stage RP. The phase 1/2 PIONEER (NCT03326336) trial is evaluating the safety and efficacy of therapy in nine patients who received a single injection of one of three GS030 doses, followed by training with the goggles 8 weeks after injection. Preliminary data of patients treated with the highest dose suggest that patients with light perception vision could locate and count objects 1 year after treatment. The trial will continue through 4 years of follow-up. An extension study is planned to recruit patients to be treated with the highest dose of GS030.[19]

BS01 (Bionic Sight) is a recombinant AAV vector that expresses an enhanced light-sensitive channelrhodopsin gene for the treatment of RP. The phase 1/2 dose-escalation trial (NCT04278131) is recruiting 20 patients with RP who will be randomly treated with one of four doses. Interim data suggest that the top four responders who received the highest dose have gained the ability to recognize shapes and objects, according to a company release. The patients' success rate for identifying objects was equivalent to guessing at baseline (25% with four choices) and ranged between 80% and 100% after treatment. The therapy pairs a one-time treatment with BS01 with the use of a device that sends signals to the light-sensitive ganglion cells.[20]

CHALLENGES AHEAD

Researchers have made remarkable progress, although several important challenges must be overcome to provide effective gene therapies. First, researchers must define which subset of viral serotypes and promoters are most effective for stable gene expression in particular retinal neurons. Second, regulators should consider streamlining the regulatory framework so that various AAV gene delivery platforms can be adapted to deliver custom treatments for rare mutations that are not present in enough patients to support clinical trials. Third, although the evidence of visual improvement has been inconclusive in some trials, intervention earlier in the course of retinal degeneration may prove more successful for the same or similar treatments. We are hopeful that these challenges will be met with the same level of commitment and enthusiasm that has put our field at the forefront of innovation in gene therapy. ■

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ORDER GENETIC TESTING LIKE A PRO

The importance of understanding various testing platforms for inherited retinal diseases.

BY JENNIFER HUEY, MS, CGC, AND DEBARSHI MUSTAFI, MD, PHD


Inherited retinal diseases (IRDs) affect approximately 1 in 2,000 to 1 in 3,000 individuals with nearly 300 genes implicated.[1,2] The AAO advocates for genetic testing for patients with a presumed IRD.[3] Early genetic diagnosis can reduce the potential for extraocular morbidity, provide patients and families with accurate recurrence risks and prognostic information, and guide treatment decisions. Unfortunately, there is no one-size-fits-all genetic test. Testing options include a phenotype-driven next-generation sequencing (NGS) panel of preselected genes, exome sequencing (ES), and comprehensive genome sequencing (GS; Figure 1). Traditionally, a tiered strategy, starting with panel-based testing, is used to reduce cost and minimize the rates of false genotyping.[4] These panels are designed to focus on smaller genomic regions and maximize the coverage of clinically relevant genes. Panel-based NGS techniques have a detection rate of 60% to 70%.[5] If this is negative, many clinicians proceed with ES to cast a wider net, while reserving GS mostly for research purposes. Clinicians should be aware that both ES and GS cost more, entail time-consuming analysis, and can identify secondary or incidental medically actionable variants, such as an increased risk for hereditary cancer or cardiac arrhythmia, which can have implications for relatives beyond a suspected retinal disease.

So, how can clinicians sift through the genetic testing landscape to select the most appropriate test for each patient? This article is designed to guide retinal specialists through this decision.

DEEP PHENOTYPING CAN GUIDE TESTING

Given the variability of IRDs in terms of pathogenesis, clinical presentation, visual symptoms, and inheritance, a thorough pretest evaluation is necessary. This can include advanced retinal imaging such as widefield fundus imaging, OCT, and electrophysiology.

There is also significant variability in the typical ages at onset of many IRDs with some associated with congenital or early-onset visual impairment while others more frequently lead to later-onset visual impairment.[6,7] A thorough clinical evaluation can provide a presumptive diagnosis and help the clinician pursue more targeted genetic testing.

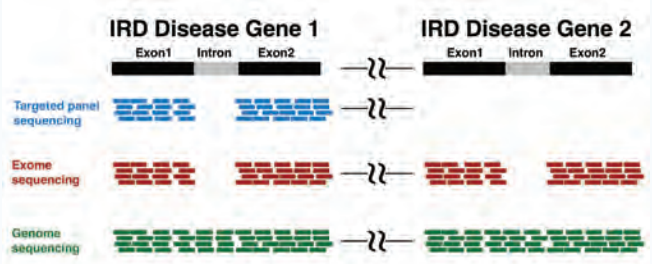

Figure 1. Schematic of the different genetic testing approaches to evaluate disease variants in IRD patients. In most targeted NGS, sequencing reads (blue) are mapped to exons, or coding regions, of targeted genes. Because the targets are preset, exonic variants in a distant (denoted by spacers) disease gene would not be captured with this test. In ES, sequencing reads (red) are mapped to exons of all genes. Both approaches are unable to capture most of the potential non-coding, or intronic disease, variants. GS, which has reads (green) encompassing all bases of an individual, can identify both intronic and exonic variants of IRD genes.

For example, a teenage male patient was referred to our pediatric retina clinic for macular edema and presumed

AT A GLANCE

- Genetic testing can include phenotype-driven next-generation sequencing, exome sequencing, or comprehensive genome sequencing.
- Disease-specific panels are a good option for patients with clear clinical phenotypes or known family history of a specific inherited retinal disease.
- Genetic testing should be provided in conjunction with comprehensive genetic counseling before and after testing.

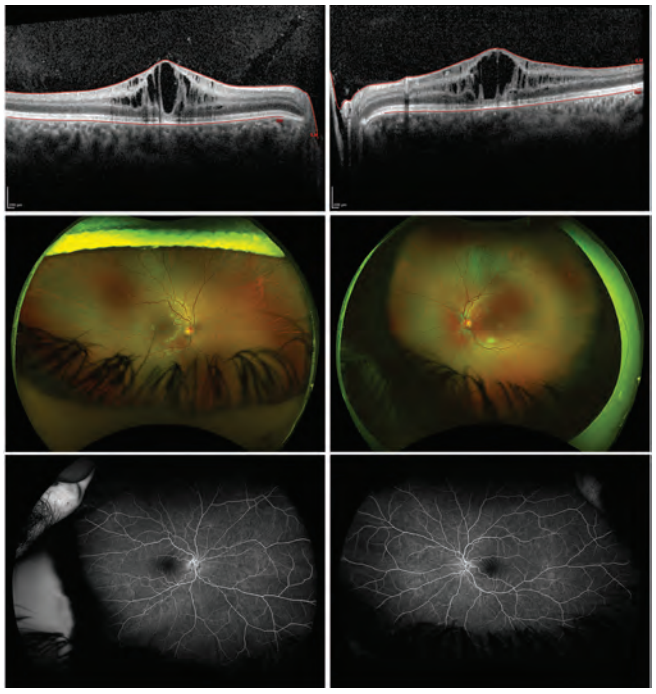

Figure 2. This teenage man presented with decreased visual acuity for presumed uveitis not controlled by topical steroid therapy. Examination revealed macular schisis cavities in each eye on OCT. Color fundus imaging revealed a blunted macular reflex but was otherwise normal. A fluorescein angiogram did not reveal leakage. This constellation of findings, along with familial history, was highly suggestive of X-linked retinoschisis, which was confirmed with genetic testing.

uveitis that had not improved with topical steroid therapy. The initial examination did not reveal any signs of inflammation, but OCT imaging showed schisis cavities and fluorescein angiography showed no leakage (Figure 2). Further history revealed that the patient had experienced blurry vision for the past few years with no signs of disease in his female siblings. The patient was started on topical carbonic anhydrase inhibitor therapy with targeted genetic testing for the X-linked retinoschisis gene *RS1*. His genetic test came back positive for a pathogenic homozygous variant in *RS1*, and his schisis cavities and visual acuity improved with continued topical carbonic anhydrase inhibitor therapy.

DISEASE-SPECIFIC, COMPREHENSIVE RETINAL, OR EXPANDED TESTING

The most common genetic test ordered for patients with a suspected IRD is panel-based NGS. Clinicians must decide between ordering a comprehensive IRD panel or a focused, disease-specific (eg, retinitis pigmentosa) panel. For patients with clear clinical phenotypes or known family history of a specific IRD, a subset of possible causative genes can be high on the clinician's differential. In such cases, disease-specific panels are a good option.

Because each NGS panel is different, clinicians should select a panel that includes coverage of disease-specific genes and those of phenotypically similar diseases to increase the likelihood of a clear diagnosis. Given the phenotypic variability of many IRD genes and the continued discovery of novel genotype-phenotype correlations,[8] many clinicians select a comprehensive IRD panel. Of note, some laboratories offer larger panels for general ocular disorders, but these do not necessarily increase the diagnostic rate, and they can increase the false discovery rate.[4]

THE GENES INCLUDED IN THE PANEL

The three commercial laboratories that offer comprehensive gene panels for IRDs (Blueprint Genetics, Invitae, and Prevention Genetics) have significant overlap with more than 250 genes shared among them. However, some genes are unique to each panel (see *Online Resource for Inherited Retinal Disease Gene Testing Panels*).[10] For example, some panels include mitochondrial genes, which have been implicated in retinal degenerations.[9] Some comprehensive retinal dystrophy panels also include genes related to ocular or oculocutaneous albinism and related retinal disorders. The addition of non-IRD-related genes in some panels changes the pretest counseling and informed consent discussion with the patient and their family.

NON-CODING VARIANTS IN IRDS

While most testing methodology focuses on the exons, or coding regions of our DNA, and the adjacent 10 to 20 base pairs that form the exon-intron boundary, we are becoming increasingly aware of the importance of deeper non-coding (intronic) variants in IRDs, most notably in *ABCA4*-related Stargardt disease.[11] Identification and characterization of non-coding variants are particularly important for patients with an autosomal recessive IRD and whose testing revealed only one disease-causing coding variant. In such populations, non-coding intronic regions of the disease gene can harbor the other allelic variant.[12] The ability to test for these non-coding variants differs greatly among the available panels, so when interpreting results, clinicians should consider if the panel included the non-coding variants in a gene of interest.

VARIANTS OF UNCERTAIN SIGNIFICANCE

Nearly any type of genetic testing will identify one or more variants of uncertain significance (VUS). A VUS is a genetic change that may or may not be associated with disease; essentially, there is not enough evidence for laboratories to predict the effect of a VUS on the gene function. These are non-diagnostic findings and should not be interpreted as causative of an IRD. Importantly, familial testing is not recommended when a VUS is identified on testing unless the laboratory states that it would be useful in reclassification of the VUS. Over time, most VUSs will be reclassified as benign/likely benign, but a few will be reclassified as likely pathogenic/pathogenic.[13]

ONLINE RESOURCE FOR GENE TESTING PANELS

Follow the QR code or visit www.mustafilab.org/resources to explore a database of genes covered by various testing laboratories.[1]

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HAVING A PERSONAL OR FAMILY HISTORY OF AN IRD CAN PLACE A SIGNIFICANT BURDEN ON THE INDIVIDUAL AND THEIR FAMILY.

GENETIC COUNSELING

Genetic testing should only be provided in conjunction with comprehensive genetic counseling, which should be done by clinicians with expertise in genetics and genetic counseling.[14] Genetic counselors should meet with the patient and family before the test is ordered to discuss the possible results, obtain informed consent, and answer any questions. Counselors should also be available to review the test results, implications, and possible next steps.

We are fortunate to have a clinic that combines IRD care with genetics to facilitate genetic testing for our patients. For clinicians who may not have genetic counselors at their clinic or institution, several companies provide genetic counseling services through telemedicine appointments, and some laboratories contract with such companies to offer genetic counseling services after testing. Having a personal or family history of an IRD can place a significant burden on the individual and their family. Better access to testing and genetic counseling can help ease that burden throughout the diagnostic process.[15,16]

FINANCIAL BURDEN

Clinicians must also consider any out-of-pocket costs to patients when deciding on appropriate testing. While patients and families often want to pursue genetic testing, many insurance companies will not cover it. To address this challenge, many laboratories have assistance programs or offer decreased self-pay prices. Some sponsored panels offer no-cost genetic testing for eligible patients (eg, the My Retina Tracker program at Blueprint Genetics and the Inherited Retinal Disease program at Invitae), although these may be a part of a research protocol, which is important to review with patients and families.

HOW OFTEN TO ORDER A GENETIC TEST

In general, patients who underwent genetic testing more than 3 years ago with normal (or inconclusive) results should be considered for updated genetic testing due to advances in gene discovery, new gene-disease associations, and updates in massively parallel sequencing technology.

KNOWLEDGE IS POWER

Ordering genetic testing for IRDs is not straightforward, as evidenced by the multitude of panels available. As clinical trials for IRDs progress to potential treatments, genetic testing will be essential to properly identify patients who may benefit from intervention. ■

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RETINA DETECTIVES: MYSTERY CASES

Rare cases are a fun way to improve your diagnostic prowess. Can you solve these mysteries?

BY SCOTT R. SHULDINER, MD; NIMESH A. PATEL, MD; SAYENA JABBEHDARI, MD, MPH; SAMI H. UWAYDAT, MD; LUÍS BERNARDES, MD; AND JOÃO PEDRO MARQUES, MD, PHD, FEBOPHTH

Everyone loves a good mystery, and retina specialists are no different. That rare "what is going on here" moment might shake up the clinical routine a bit, but it also helps hone your diagnostic skills. The mystery cases presented here are designed to help you stay on your toes and prepare for the next patient who presents with unexplained retinal findings.

– Rebecca Hepp, Editor-in-Chief


MYSTERY CASE NO. 1

By Scott R. Shuldiner, MD, and Nimesh A. Patel MD

A young adult woman was referred in the setting of abnormal retinal findings, although she was asymptomatic. Her last eye examination had been 10 years prior. On initial examination, her BCVA was 20/20 OD and 20/30 OS. Her dilated fundus examination was significant for 360° peripheral retinal hyperpigmentation (Figure 1). OCT imaging revealed outer plexiform deposits in the macula of each eye (Figure 2). Fundus autofluorescence (FAF) showed hypofluorescence in areas of atrophy in the periphery and punctate areas of hyperfluorescence in the areas of the deposits (Figure 3). Visual fields were full bilaterally.

During a detailed review of systems, the patient endorsed mild but progressive exertional chest pain for the last 3 months. A cardiology referral was initiated, where an echocardiogram demonstrated severe symmetric hypertrophic cardiomyopathy.


MYSTERY CASE NO. 2

By Sayena Jabbehdari, MD, MPH, and Sami H. Uwaydat, MD

A 37-year-old White man presented for evaluation of progressive worsening of vision over several years. The patient reported seeing wavy lines and occasional blurring of letters. He also complained of floaters in each eye. His past medical history included diabetes, hypertrophic cardiomyopathy, skeletal myopathy/exercise intolerance, deafness, and depression. His past social history was unremarkable.

On examination, his BCVA was 20/50 OD and 20/25 OS. IOP was normal, and the anterior segments were unremarkable. Fundus examination revealed pigmentary changes in the macula along the arcades in each eye. OCT revealed focal loss of outer retinal layers in each eye (Figure 4).


MYSTERY CASE NO. 3

By Luís Bernardes, MD, and João Pedro Marques, MD, PhD

A 57-year-old woman was referred for diabetic retinopathy (DR) screening. She had been diagnosed with diabetes at age 30, and her last ophthalmic observation was 3 years prior after undergoing cataract surgery in the left eye. Her history was positive for arterial hypertension and hearing loss. The patient said that her mother had hearing difficulties and low vision, presumably due to cataract.

The fundus examination revealed bilateral peripapillary atrophy along with patchy areas of chorioretinal atrophy (Figure 5A and 5B). A high degree of inter-eye symmetry was noted. FAF showed macular speckled hyper- and hypoautofluorescence (Figure 5C and 5D). This was also noted on near-infrared reflectance (Figure 5E and 5F); on OCT, atrophy of the outer retinal layers and retinal pigment epithelium (RPE) was present in the topographical location of the patchy atrophic lesions (Figure 5G and 5H).

See the discussion on page 34 for the diagnosis in each case.

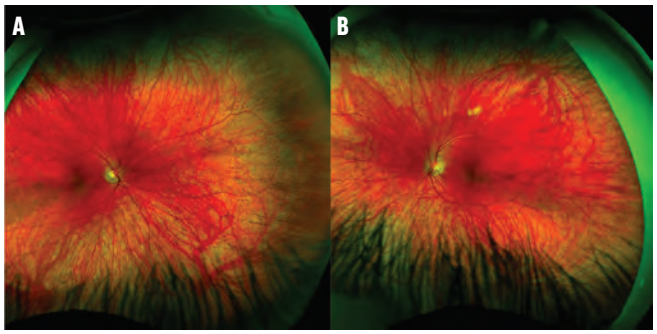


Figure 1. The fundus examination revealed 360° peripheral retinal hyperpigmentation in the right (A) and left eye (B).

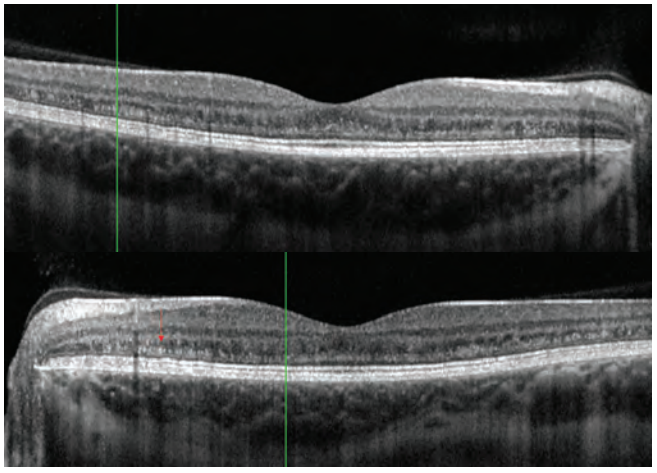


Figure 2. OCT imaging was remarkable for outer plexiform deposits (red arrow) in the macula of each eye.

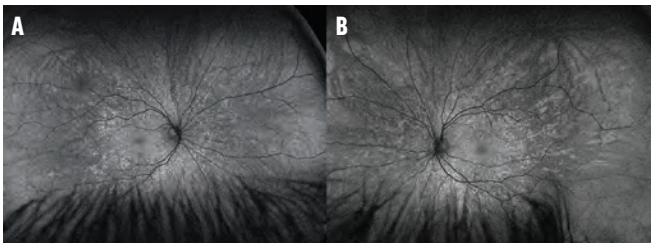


Figure 3. In the right (A) and left (B) eye, FAF showed hypofluorescence in the areas of atrophy and punctate areas of hyperfluorescence in the area of the deposits.

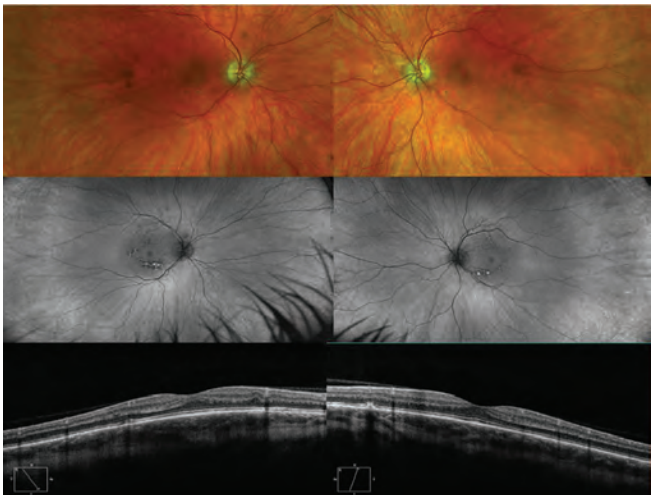


Figure 4. Fundus photography showed pigmentary changes in the macula and along the arcades of each eye. FAF shows a curvilinear hyperfluorescent area around the macula surrounded by an indistinct hypofluorescent pattern in each eye. OCT reveals focal loss of outer retinal layers in each eye.

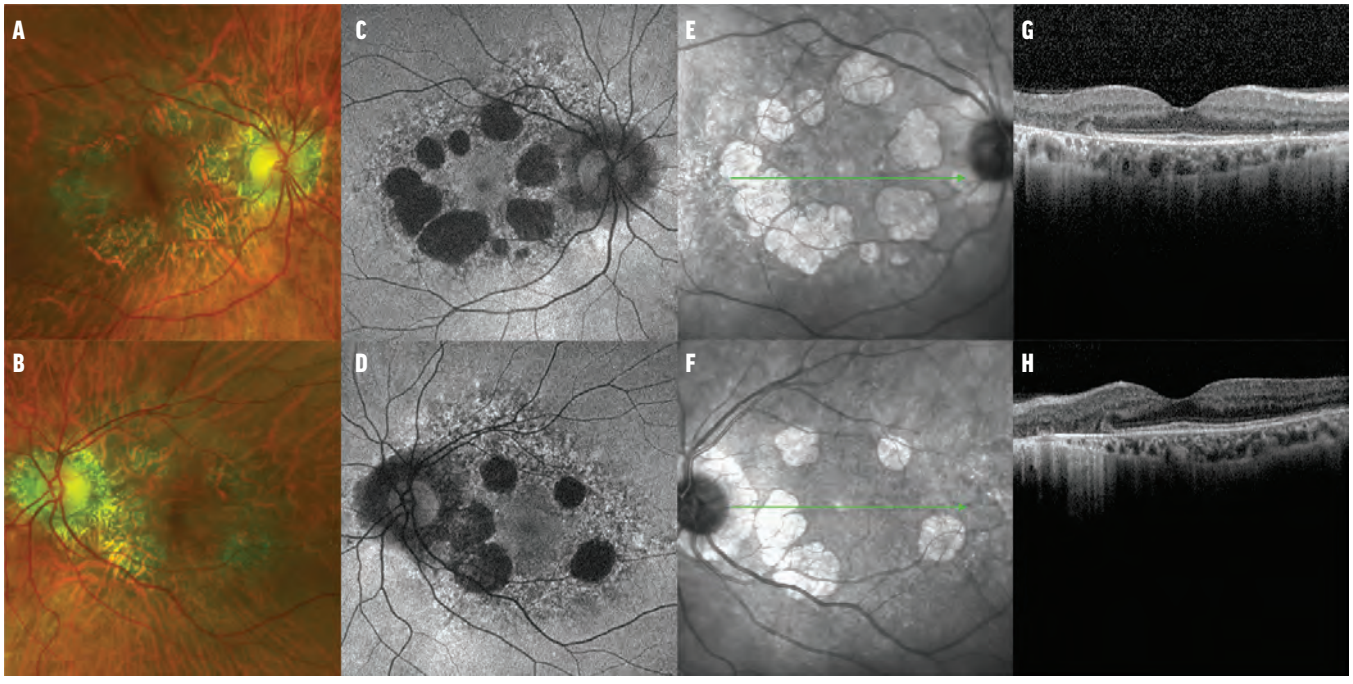


Figure 5. Fundus imaging showed bilateral peripapillary atrophy along with patchy areas of chorioretinal atrophy in the posterior pole, sparing the fovea (A and B). FAF showed macular speckled hyper- and hypoautofluorescence, outlining the patchy atrophy (C and D). This was also noted on near-infrared reflectance (E and F). OCT showed atrophy of the outer retinal layers and RPE in the topographical location of the patchy atrophic lesions (G and H).

DISCUSSION

Case No. 1: Danon Disease

Genetic testing was positive for an X-linked pathogenic variant in the *lysosome-associated membrane protein-2* (*LAMP2*) gene (c864+1G>T, Intron 6). Based on the patient's genetic mutation and history of hypertrophic cardiomyopathy, she was diagnosed with retinal dystrophy in the setting of Danon disease.

Danon disease is a rare X-linked lysosomal glycogen storage disease with the classic triad of cardiomyopathy, myopathy, and variable intellectual disability. In the absence of treatment, patients experience supraventricular arrhythmias and are at risk for sudden death before the age of 30; defibrillators and heart transplantation have significantly improved life expectancy.[1] *LAMP2*, a glycoprotein that plays a critical role in lysosomal biogenesis and phagosome maturation, is part of a growing number of genes associated with retinopathy. The phenotype of Danon disease may also include a diffuse cone-rod dystrophy and other maculopathies.[2] Ophthalmic manifestations are common and may affect a variety of structures with signs including corneal clouding, optic atrophy, glaucoma, retinal degeneration, and decreased electroretinogram wave amplitude.[3,4] Recent studies suggest that patients with Danon disease show progressive and diffuse retinal and macular degeneration changes, including pigmentary disturbances and discrete sub-RPE deposits.[5] The long-term prognosis for carriers of *LAMP2* mutations is not known, and there is a need for serial retinal examinations and electrophysiology testing to monitor for progression.[6]

Our patient continues to be monitored for progression. Since this time, a pacemaker and implantable cardioverter-defibrillator have been placed to prevent arrhythmias.

Case No. 2: MELAS

Genetic testing revealed a pathogenic mutation in the *mt-TL1* gene (m.3243A>G) with a heteroplasmy of 55.5%. This genetic mutation is classically associated with mitochondrial encephalopathy, lactic acidosis, strokes/stroke-like episodes (MELAS) syndrome, and maternally inherited diabetes and deafness (MIDD).[7,8]

MELAS syndrome is a maternally inherited condition that impairs the oxidative phosphorylation/ATP production.[7] Patients usually present with seizures, short stature, stroke-like episodes, lactic acidosis, deafness, episodic vomiting, and proximal muscle weakness before the age of 40.[9,10] The common ocular manifestations of MELAS include ptosis, ophthalmoplegia, myopia, retinal pigment mottling, chorioretinal atrophy, nuclear cataract, and optic atrophy due to the high metabolic activities in the affected mitochondria.[11] Pigmentary retinopathy involving mainly the posterior pole and midperiphery of the retina is the most common ocular manifestation of MELAS. However, the retinopathy can range from mild "salt and pepper" retinopathy to severe bone spicules with RPE atrophy.[12] The histologic changes include depigmentation and hyperpigmentation of the RPE, photoreceptor degeneration, ganglion cell loss, and degeneration of the choroid.[13-15]

Our patient was unable to tolerate the prescribed mitochondrial oral cocktail (L-carnitine, co-enzyme Q, thiamine, riboflavin, nicotinamide, biotin, and L-creatine); at the last follow-up, his BCVA had decreased to 20/60 OD and 20/40 OS.

Case No. 3: MIDD

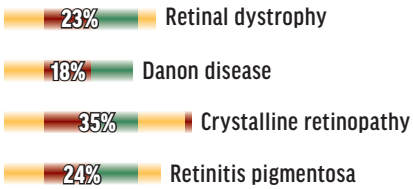
Given the clinical picture and imaging findings, the patient underwent mitochondrial DNA sequencing. The m.3243A>G variant on the *mt-TL1* gene was found in heteroplasmy, confirming a diagnosis of MIDD. After 2 years of follow-up, no significant progression of the atrophic lesions was observed, and the patient remains asymptomatic.

MIDD has an estimated prevalence of 1 to 9 in 1,000,000 individuals.[7] The hallmarks of disease include early-onset insulin-dependent diabetes/impaired fasting glucose, progressive sensorineural hearing impairment (usually

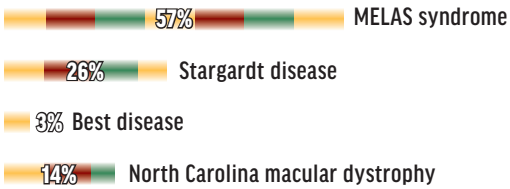
WE ASKED, YOU ANSWERED

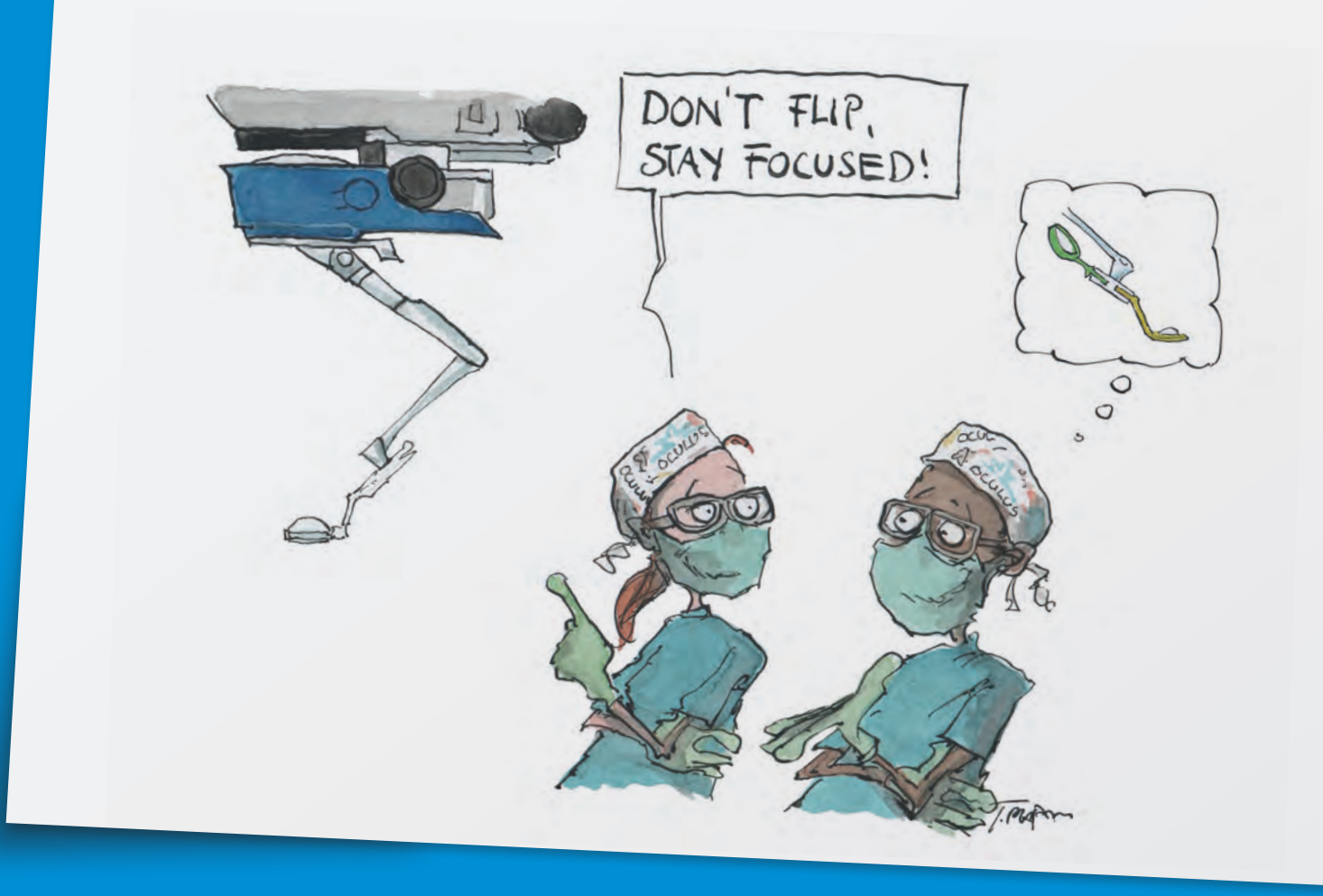
We took to social media to see if retina specialists could sleuth out the answer to these mystery cases. How well did you do?

Case No. 1 Social Media Poll Results:



Case No. 2 Social Media Poll Results:





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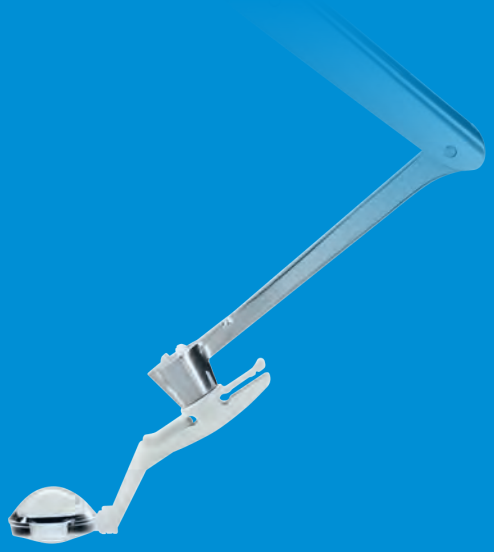

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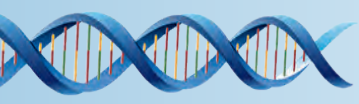

WE ASKED, YOU ANSWERED

We took to social media to see if retina specialists could sleuth out the answer to these mystery cases. How well did you do?

Case No. 3 Social Media Poll Results:

- 17% Atrophic AMD
- 33% *PRPH2*-related macular dystrophy
- 16% Late-onset Stargardt disease
- 34% Maternally inherited diabetes and deafness

preceding the onset of diabetes), maculopathy, and a normal/low body mass index.[16-18] Additionally, patients with MIDD may have short stature, proximal limb myopathy, left ventricular hypertrophy, renal failure, and gastrointestinal disease.[7] Interestingly, DR is considerably less common than that in other forms of diabetes.[16]

Most affected individuals harbor the m.3243A>G mutation in the *mt-TL1* gene, the single most common pathogenic mitochondrial variant.[19] Because mutations occur in the mitochondrial DNA, maternal inheritance is observed.[17] However, no clear correlation exists between mutational load (heteroplasmy) and phenotypic expression/severity.[18]

Most patients are asymptomatic and diagnosed based on clinical findings, such as pattern dystrophy-like changes and slowly progressive patchy atrophy of the RPE, localized at the posterior pole and frequently involving the peripapillary area.[16,17,20] The fovea is often preserved, thus conferring a favorable functional prognosis to most patients. No proven intervention is available for MIDD-associated maculopathy, but regular screening for traditional diabetes-related microvascular complications is advisable. Early coenzime Q10 supplementation has shown promise in preventing hearing loss and delaying progression in diabetes.[21] ■

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GLOBAL RETINA CARE

GLOBAL RETINA CARE: THE UKRAINE EXPERIENCE

Volunteering in a war-stricken country comes with significant challenges—some expected, others less so. Here's one retina surgeon's story.

BY REBECCA HEPP, EDITOR-IN-CHIEF, WITH PAUL RUNGE, MD

Imagine seeing two patients with Usher syndrome, a child with Stargardt disease, a young boy with juvenile X-linked macular schisis, a 5-year-old girl with von Hippel Lindau syndrome, and an 11-year-old boy with an optic nerve pit and macular edema—all in one day. Now envision being a volunteer retina specialist in a country at war. That's what Paul Runge, MD, has been dealing with during his trips to Ukraine. He has also seen patients with retinitis pigmentosa, Best disease, Leber congenital amaurosis with perimacular lacunae, fundus flavimaculatus, and fundus albipunctatus. If he were staffing an inherited retinal disease clinic, this might not seem so out of place, but these are the types of patients who are walking into the routine pediatric retina clinic at the children's hospital in Ivano-Frankivsk, a little over 80 miles from Lviv, Ukraine (Figure).

This isn't exactly the experience Dr. Runge was expecting when he decided to volunteer in Ukraine. "Most of the cases I have seen in Ukraine are what I would describe as bread-and-butter ophthalmology—diabetic retinopathy, macular degeneration, chronic open-angle glaucoma, cataracts, retinal detachments, and retinopathy of prematurity (ROP)," he told *Retina Today* in an interview. "But I have been very surprised at the number of genetic retinal conditions I have seen in a relatively short period of time."

HEARING THE CALL

Dr. Runge had just retired in January 2022 (after working with Steve Charles, MD, in Memphis), and was sitting at home watching the war unfold.

"I thought that there might be something I could do to help, and I began sending emails to hospitals and clinics in western Ukraine," he explained. He eventually connected with Roman Fishchuk, MD, an ear, nose, and throat surgeon in Ivano-Frankivsk in southwestern Ukraine, who has since orchestrated all of Dr. Runge's connections.

"I didn't know what to expect, but I was happy to get involved in any way, be that emergency room or retina," he admitted. "In fact, I ordered a bulletproof vest."

HELP ON THE WAY

Despite those initial misgivings, the vest is long forgotten in a closet somewhere, replaced by slit lamps, laser indirect ophthalmoscopes, and anti-VEGF injections. Patient care in the Ukraine is similar to the care provided in western Europe or North America, he said, but air raid sirens often disrupt the hustle and bustle of the clinic. Some still head to the bunker, Dr. Runge said, but just as many don't even bother, instead choosing to stick with their rounds. Dr. Runge quickly found a place for his expertise in pediatric retina and began noticing ways that he could be helpful, and possibly even implement a few improvements.

"Change in the Ukraine, as in most places, happens gradually," he admitted. "These doctors have been providing effective care for many years without my help, and by taking the time to listen and learn from these successful physicians, I can hopefully help improve their situation incrementally."

And he certainly has. One of his first accomplishments was securing a Norlase laser indirect ophthalmoscope (LION) to treat threshold ROP at the children's hospital.

"The doctors light up, and you see how excited they are," he said of the experience of introducing the laser to the team. As the first surgeon in the Ukraine to perform this

AT A GLANCE

- Paul Runge, MD, has been volunteering in the Ukraine since the war broke out in early 2022.
- In addition to diabetic retinopathy, macular degeneration, and retinopathy of prematurity, he has seen many genetic retinal conditions.
- Dr. Runge is working with a programmer to create an app to help improve the medical record system in the Ukraine, particularly for pediatric patients treated for retinopathy of prematurity.

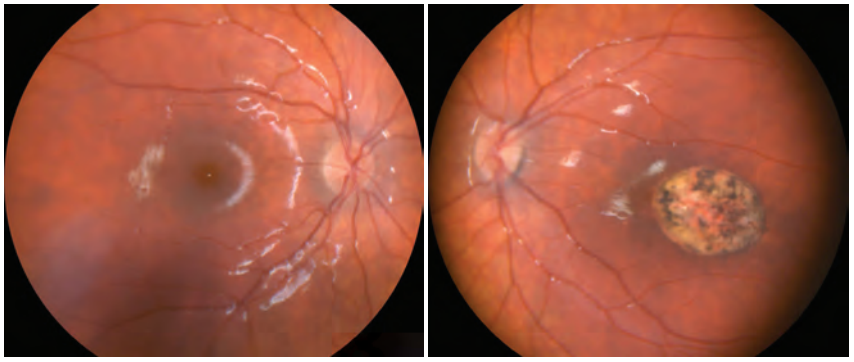

Figure. While in the Ukraine in May 2023, Dr. Runge cared for this 10-year-old boy with congenital toxoplasmosis and a perimacular scar in his left eye.

laser treatment using the LION, Dr. Runge quickly gained the attention of attendings at the local university who treat patients with diabetes. They don't have a good laser option, either, and are eager to share this one, or possibly source a new one for themselves. Dr. Runge is already planning to get more involved in the university's diabetic endocrinology clinic and help them perform panretinal photocoagulation treatment for patients in need.

Another stark difference that took some getting used to for Dr. Runge is the health record situation. Patients are in charge of their own medical records, he noted. "A little notebook contains all their medical records, including tests, and they bring this notebook with them to their appointments, and they have the only copy," he explained. This has obvious drawbacks, particularly for ROP patients, and Dr. Runge set out to do something about it.

"I've been talking to a programmer in Berlin, and he is putting together an app that will allow us to input basic information about the pediatric patients and then do some tracking," he said. If that is successful, Dr. Runge is hopeful that the app will evolve into an open-source electronic health record for the entire country.

EDUCATION

Dr. Runge wasn't surprised to find that most of the medical equipment has been around the block a time or two, considering that the same was true when he volunteered in Russia early in his career—and not much had changed. Thus, his first few trips involved supplying the clinic with used indirect ophthalmoscopes and diagnostic lenses. At least a few offices have access to OCT and OCT angiography (and patients show up with the printouts in their little booklets). "The scans were of fairly good quality, but in many instances, there were issues with interpretation of the tests," Dr. Runge said. "Patients get the scans done but they don't get a great explanation about what was found. The ophthalmologists are well trained, but they sometimes don't have the exposure that we have with interpreting OCTs and OCT angiography."

Dr. Runge began providing hands-on lectures to the medical students (they have 450 of them). Students and attendings alike are known to show up with OCT scans in hand to ask for help interpreting the findings, he said. Their enthusiasm has rejuvenated Dr. Runge's career, and he now spends a significant portion of his trips teaching.

UNMET NEEDS

Dr. Runge knows there is much work to be done. He is still on the hunt for good quality slit lamps for many of the clinics he visits, the app is working its way through the development stages, and the students are chomping at the bit for more hands-on experience.

The education is crucial for future practitioners, and the laser helps patients with ROP and diabetic eye disease, but what about those patients streaming through the clinic with rare inherited diseases? They remain a population in need, according to Dr. Runge. For most patients in the Ukraine, genetic testing is out of the question; usually a trip to Poland or Italy is the only path toward a definitive genetic answer. Recently, however, a patient with retinitis pigmentosa gained access to the Invitae inherited retinal disorders panel in Kyiv—a breakthrough Dr. Runge is hoping to capitalize on to add that service to the children's hospital in Ivano-Frankivsk.

"Now that new treatments are being developed for these conditions, and because a genetic diagnosis is a requirement to receive treatment or to be entered into a clinical trial, it is essential that genetic testing be made available to our patients," Dr. Runge emphasized.

STAY HUMBLE

While Dr. Runge plugs away at small advances that can make a world of a difference, he is careful to remember one thing. "These doctors have been practicing medicine for years without my help, and they are brilliant and motivated and only need a little nudge in one direction or the other to take off," he observed. "The last thing you want to do is to go into these situations like a bull in a China shop and tell everyone that they aren't doing it right." Instead, take a step back, listen to their needs, and then find little ways to implement incremental changes that are the most helpful, he suggested.

"Only then can you offer global solutions to certain problems," he offered. ■

PAUL RUNGE, MD

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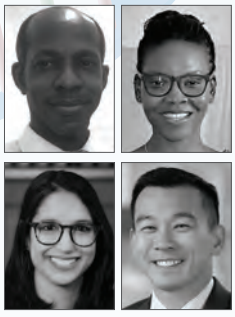
GLOBAL RETINA CARE

GLOBAL RETINA CARE: UVEITIS IN WEST AFRICA

Progress, challenges, and the future of retina care in Sierra Leone.

BY LLOYD HARRISON-WILLIAMS, MD; JALIKATU MUSTAPHA, MD; JESSICA G. SHANTHA, MD, MSC; AND STEVEN YEH, MD



Uveitis is a common eye condition in West Africa that can lead to blinding complications if not promptly diagnosed and effectively treated. Studies in Sierra Leone have shown that, after cataract, uveitis is the major cause of blindness.[1] While the association with infectious disease (eg, toxoplasmosis, syphilis, varicella zoster, and herpes simplex) predominated in prior epidemiologic studies in Sierra Leone, the widespread availability of laboratory diagnostics to ascertain these diagnoses was limited.[2]

More recently, our research group and others have assessed the spectrum of uveitis in Ebola virus disease (EVD) survivors in Sierra Leone and Liberia. The high rate of uveitis—between 18% and 34%—suggests the potential effect of uveitis in EVD survivors.[3-6] Importantly, a closer look at uveitis in EVD survivors and further examination of patient populations revealed broader areas of unmet need in education and awareness of uveitis and its complications for eye care personnel and the general medical community.

SCREENING AND CARE DELIVERY

Because of limited access to ophthalmologists and eye care professionals in Sierra Leone and many other West African countries, most patients are initially screened at a community level by ophthalmic nurses. Limited equipment may preclude the ability to assess very subtle eye conditions, including the early stages of uveitis. For example, the equipment may be limited to a vision chart, penlight, and a direct ophthalmoscope. While these tools can effectively diagnose dense white cataractous lenses, posterior synechiae, pupillary membranes, and corneal scarring, they may not allow the diagnosis of early stages of uveitis with findings such as anterior chamber cell/flare and anterior vitreous cell.

Combined with the high volume of patients in screening programs and limited equipment availability in some community based settings, the clinician's ability to properly diagnose the early stages of uveitis may be hampered. Most patients present only when complications of uveitis have commenced, such as severe pain, redness, photophobia, or vision impairment that may be challenging to reverse. In developing countries, such as Sierra Leone, the importance of careful clinical assessment cannot be overestimated.

Despite these ongoing limitations, progress has been made through increased education and a more robust understanding of uveitis because of clinical experience with toxoplasmosis, EVD, and HIV-associated infectious diseases. In Sierra Leone in particular, the use of advanced ophthalmic imaging, such as ultra-widefield fundus photography and OCT, has allowed clinicians to more objectively document uveitis and retinal disease in patients with ocular inflammation. Additional resources through Ministry of Health and Sanitation (MOHS) laboratories, including Quantiferon-TB Gold testing, have also improved eye care providers' ability to detect latent tuberculosis, which can also be associated with uveitis.

AT A GLANCE

- The authors found a high rate (between 20% and 25%) of uveitis in patients diagnosed with Ebola virus disease in Liberia.
- Limited patient access to trained care providers, supplies, and diagnostic technology hamper clinicians' ability to properly diagnose the early stages of uveitis in patients in West Africa.
- Although research infrastructure has improved the region's subspecialty service delivery, remaining challenges include patient-level and health system constraints that require strengthening.

Figure. OCT imaging and fundus photography performed at Connaught Hospital in Sierra Leone (A). Slit lamp biomicroscope at the Lowell and Ruth Gess Eye Hospital, also in Sierra Leone (B). Photos obtained with patient consent.

LESSONS FROM EBOLA

During the West African EVD outbreak from 2014 to 2016, our research group and others evaluated patients with EVD in Liberia and Sierra Leone, in collaboration with MOHS ophthalmologists and nongovernmental organizations. We found that 20% to 25% of EVD survivors in Liberia had uveitis.[3] Moreover, the PREVAIL III study, an NIH-funded study that evaluated EVD survivors compared with close contacts, showed that while EVD survivors showed a high prevalence of uveitis (26%), close contact patients also showed a high prevalence of uveitis at 12%.[4] These results from Liberia indicate a high baseline prevalence of ocular inflammation that warrants further assessment. EVD-associated uveitis is particularly vision-threatening. Specifically, more than 60% of eyes demonstrated vision impairment and nearly 40% met World Health Organization criteria for blindness (ie, VA of 20/400 or worse) at the time of uveitis diagnosis during EVD convalescence.[3]

We also observed gaps in clinical infrastructure, ophthalmic imaging, uveitis subspecialty training, and consumable items (eg, clinic supplies and ophthalmic medications). In total, these gaps made the diagnosis and management of complex uveitis syndromes particularly difficult. While discovering the association between uveitis and EVD was critical to the field's understanding of EVD survivorship and the risk of vision impairment from uveitis, vision health systems must be equipped to care for uveitis and its sequelae.

ETIOLOGIES AND ONGOING NEEDS

More recently, our collaborative group conducted a cross-sectional epidemiology uveitis study.[7] The study of 132 patients with uveitis in Sierra Leone showed that panuveitis was the predominant anatomic location (n = 51, 40%), followed by posterior uveitis (n = 36, 28%). Most patients (59%) were considered to have active uveitis at their initial presentation, and 40 patients (31%) showed bilateral disease. Of note, the mean VA of eyes affected with uveitis was 6/60 (Snellen VA of 20/200), and blindness (defined as VA of 3/60 or worse) was observed in 55 eyes (33%) with uveitis. Based on clinical assessment and laboratory services available in Sierra Leone, undifferentiated etiologies comprised most cases (n = 69, 53%), and toxoplasmosis was observed in a significant minority of patients (n = 47, 37%), while traumatic uveitis was also notable (n = 7, 5%). Based on these high levels of vision impairment, further research into the reasons for delayed presentation, etiologies of uveitis, and associated systemic diseases are warranted.[7]

TREATMENT PARADIGMS

Given the high rate of toxoplasmosis in the recent observational study and prior epidemiology work, initiation of antitoxoplasmosis therapy based on a clinical impression and provisional diagnosis is often the first treatment approach. Given the high rate of vision impairment at presentation, secondary complications, such as posterior synechiae, cataract, and vitreous opacity, often have already developed. Empiric treatment for toxoplasmosis includes cotrimoxazole tablets and pyrimethamine tablets, which are the most common and affordable medications. However, pyrimethamine has been used more recently for malaria prophylaxis and is now becoming difficult to acquire.

To complicate treatment further, patients often defer laboratory testing and radiologic imaging when these services are available on a fee-for-service basis because of the high prevalence of poverty. However, HIV serology is offered free of charge in most government hospital laboratories, and this is routinely requested for all our patients with uveitis of unknown etiology. The Treponema pallidum hemagglutinin test is also affordable and available for patients with uveitis, and blood glucose is checked, particularly for patients who require systemic corticosteroids.

For patients with presumed uveitis of noninfectious origin, oral corticosteroids may be used but only after proper counseling and consideration of other comorbidities, such as diabetes. Oral prednisolone tablets are used with a once-daily dose of 1 mg/kg body weight in the morning with

meals. The latter directive is critical, as some patients cannot afford three daily meals. Additional medications, such as omeprazole, may be added based on past medical history or gastroesophageal reflux disease.

UNIQUE CHALLENGES IN DEVELOPING COUNTRIES

Following initiation of therapy, several patient-specific factors can be problematic, such as the affordability of repeat patient visits, transportation issues (including travel during the rainy season), and loss to follow-up. Further work on the reasons for nonadherence to therapy and follow-up are ongoing but are unique to each clinical setting and geography (eg, challenges with transportation to urban centers from distant, rural provinces due to rainy season and cost).

When caring for this population, clinicians must carefully judge each patient's true socioeconomic status because patients often go to great lengths to drive down their costs of care. For example, a high- or middle-class family with an ill child may have a poorer relative or maid bring the child to the hospital to conceal their true socioeconomic status. Local partnerships and an understanding of the socioeconomic context can help to establish tiered levels of payment and research, which means patients are assessed regardless of socioeconomic status prior to appropriate care referral.

INFRASTRUCTURE, HUMAN CAPITAL, AND TRAINING

Given the challenges of uveitis care and the Sierra Leone experience, investment in ophthalmic infrastructure and the development of human capital, including physician and nonphysician ophthalmic personnel, is needed. For example, OCT and widefield fundus photography were unavailable 2 years ago but are now being used for the Sierra Leone MOHS and Lowell and Ruth Gess Eye Hospital Ebola Survivor study, which assesses the long-term ophthalmic manifestations of EVD in survivors in Sierra Leone (Figure). This existing research infrastructure may be used for additional uveitis and ophthalmic subspecialty research initiatives. Moreover, the existence of ophthalmic research equipment infrastructure and supplies, as well as the introduction of research processes, now provide additional skills through teaching scope availability, clinical care, and opportunities for training in scientific methodology.

FUTURE ENDEAVORS

Uveitis management in Sierra Leone and developing countries with a high rate of infectious diseases—including toxoplasmosis and EVD-associated uveitis—has provided a wealth of information about infectious pathologies and opportunities to provide complex care to underserved populations. The introduction of research infrastructure has improved the region's ophthalmic imaging capabilities, research workflows, ophthalmic education, and ophthalmic subspecialty service delivery. However, remaining challenges include patient-level considerations (ie, treatment adherence, financial constraints, and delayed presentation) and health system constraints (ie, availability of molecular diagnostic testing for infectious disease syndromes, supply chain, and reagents for serologic testing).

Such constraints emphasize the need for strong clinical observation skills and empiric treatment and task-shifting to mid-level health care providers to allow ophthalmologists and optometrists to deal with rare or severe conditions. This can give the clinician more time to engage in further research, training, monitoring, and supportive supervision to build, improve, and sustain a robust health care system. ■

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RISING STARS IN RETINA

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

Hasenin Al-khersan, MD

Retina Today: When did you first know that you wanted to become a retina specialist?

When I was about 7 years old, my uncle lost his vision due to an occipital tumor. Seeing how his life completely changed was jarring, and the experience left me feeling powerless. That feeling stuck with me and motivated me to pursue vision research in college, which happened to be in retinal cell physiology. I was fascinated by the infinite complexity arising from such delicate tissue. To pair my interest in ocular physiology with the ability to make a direct clinical effect on patient care was a dream. From that moment on, I was hooked and never looked back.

_RT_: Who do you look to as mentors in the field?

I am privileged to be surrounded by an amazing cast of mentors at Bascom Palmer. Audina Berrocal, MD, in particular, has been an incredible mentor. She sets an example of what it means to be a compassionate physician, an inquisitive clinician, and an authentic and genuine person. Dr. Berrocal has been someone I've turned to throughout my residency and fellowship, and I feel lucky to be able to call her a mentor and friend.

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

We are fortunate at Bascom Palmer to operate completely independently during our second year of fellowship, which is our Chief Resident year. I'll forever remember the first case that I performed alone, a scleral buckle in a young patient with a macula-on detachment.

It was the culmination of more than a decade of studying and training, and it felt incredibly gratifying to be able to put into practice all that I had learned for the benefit of the patient.

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

Patient care remains at the core of the practice I hope to grow. Seeing and caring for patients brings me great fulfillment. Additionally, ophthalmology (really, the world) is at the precipice of an artificial intelligence (AI) revolution. I hope to partake in the incorporation of new AI-driven technologies within retina. These AI tools, if crafted responsibly, may be able to help us amplify our clinical effect in ways we may not yet even imagine.

FIRST CAREER MILESTONE

Dr. Al-khersan is joining Retina Consultants of Texas in Houston.

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

Always remember the why behind your journey in medicine and ophthalmology. We are incredibly privileged to be entrusted with the care of patients, many of whom come to us at perhaps their most vulnerable. During training, even when things get busy, don't forget to see the patient in front of you. It may be easy to say but sometimes hard to do in an era of crushing bureaucracy and high patient volumes. Despite that, we have the responsibility to make a profound difference in our patients' lives. ■

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GLOBAL RETINA CASES: TURKEY

PLEASANT SURPRISES IN THE PEDIATRIC OR


Lessons in never giving up, even when the presentation seems hopeless.

BY ŞENGÜL ÖZDEK, MD, FEBO, FASRS, AND ECE ÖZDEMIR ZEYDANLI, MD, FEBO, FICO

Perseverance is one of the most important qualities a medical professional possesses, particularly when treating children. In challenging cases—such as when a child's ocular presentation is highly disconcerting or surgical intervention seems unlikely to succeed—there may be a temptation to abandon efforts. However, it is crucial to remember that during surgery, unexpected outcomes and pleasant surprises are possible. Even eyes that appear inoperable can, in some instances, be salvaged.

Our work with pediatric eye conditions has presented many instances where an eye was deemed inoperable and beyond hope—only for us to discover that the condition was less severe than initially thought. With appropriate treatment and surgical intervention, some eyes not only avoid significant complications but even demonstrate functional improvement. In this article, we review two such cases.

CASE NO. 1

A 7-month-old boy presented with unilateral leukocoria and retrolental and vitreous hemorrhage. This eye was previously considered inoperable due to a presumed closed-funnel retinal detachment (RD) detected with ultrasonography for an unknown etiology (Figure 1). The fellow eye was normal.

A detailed history revealed that the visual impairment had been noticed very early in the first weeks of life. Careful examination and ultrasonography provided additional insights that led us to a diagnosis of persistent fetal vasculature (PFV) and tractional RD with extensive retrolental and vitreous hemorrhage. After explaining the very low expectations of the surgical outcome in detail to the family, we decided to proceed with surgery. The corneal diameters were 11.5 mm x 11.0 mm for both eyes.

We performed a limbal lensectomy and vitrectomy, revealing a multirooted hyaloidal stalk and a tent-like tractional RD. Peeling the membranes resulted in an attached retina, including the macular area, with extramacular folds in the nasal retina. As was true in this case, the presence of dense hemorrhages accompanying a hyaloid stalk may resemble the appearance of a closed-funnel RD.[1,2] Given their mostly unilateral nature, these cases can be deemed inoperable. However, surgical intervention proved successful in this case, resulting in good anatomy, release of tractions, an attached macula, and the ability to fix and follow light, as we would expect in tent-like posterior PFV cases.[3]

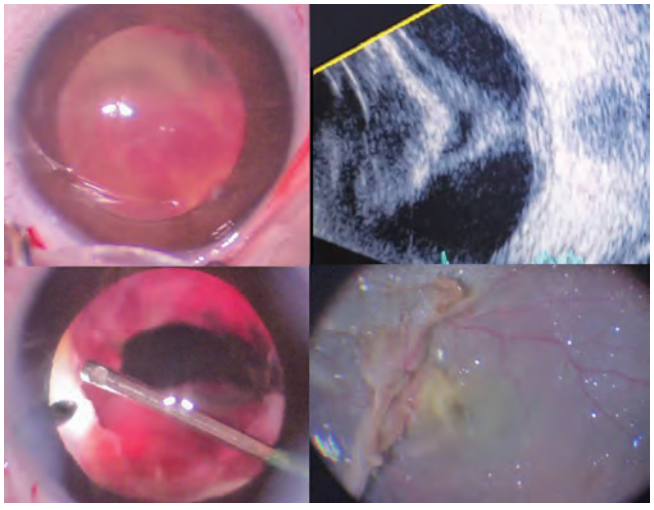


Figure 1. This patient with posterior PFV presented with retrolental and vitreous hemorrhage, mimicking a closed-funnel RD on B-scan ultrasonography. A limbal lensectomy and vitrectomy, followed by layer-by-layer removal of dense hemorrhagic membranes, uncovered a hyaloid stalk extending from the optic nerve head and forming retinal folds in all directions. The surgery resulted in an attached retina including the macula except from the narrow retinal folds in the nasal area.

CASE NO. 2

A 10-month-old boy presented with bilateral leukocoria, severe anterior segment dysgenesis, glaucoma, and no light reaction in either eye (Figure 2; Video). Several practices had considered these eyes inoperable. The patient had high IOP (35 mm Hg OD and 40 mm Hg OS), a cloudy cornea, and buphthalmia with corneal diameters of 16 mm OD and 17 mm OS. He also exhibited dysplastic iris and angle structures, rubeosis iridis and lentis with extensive peripheral anterior synechiae, total iridocorneal apposition causing partial corneal opacities, and fibrovascular tissue covering

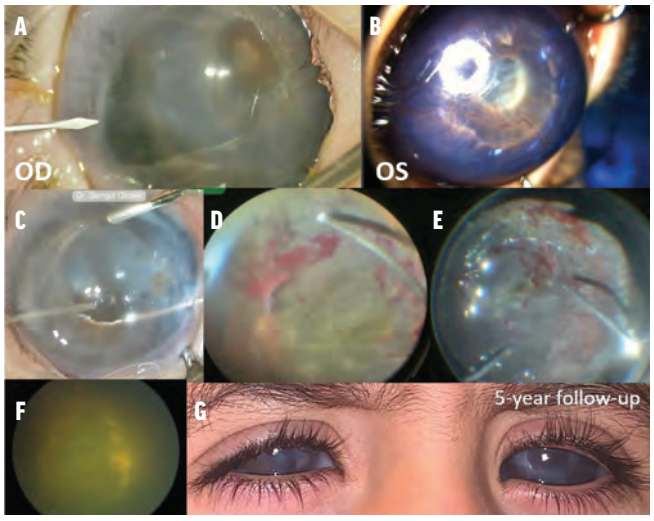


Figure 2. This 10-month-old boy presented with severe bilateral anterior segment dysgenesis and glaucoma (A, B). Ultrasonography revealed bilateral multifocal tractional RD and vitreous opacities. The patient underwent vitrectomy in each eye, which included extensive synechiolysis, pupilloplasty, removal of tractional membranes, and laser photocoagulation of the avascular peripheral retina (C, D, and E). Following the surgery, the patient achieved ambulatory vision in each eye (F). Although the cornea was cloudy, he maintained ambulatory vision during the 5-year follow-up period (G).

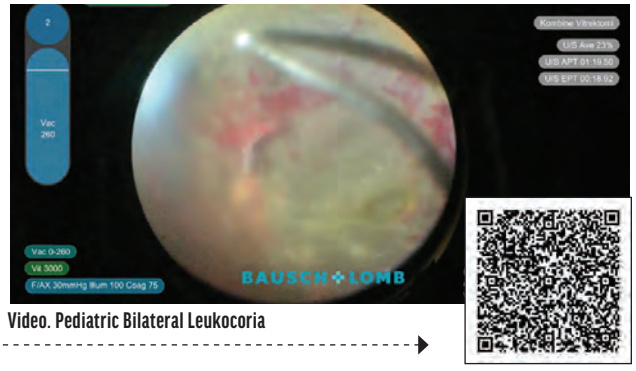
the pupillary area. Ultrasonography revealed vitreous opacities and membranes causing local tractional RDs at multiple points of the posterior pole in each eye.

Cases with severe anterior segment dysgenesis tend to be considered inoperable when accompanied by posterior segment pathology.[4,5] Without treatment, they usually end up with total corneal opacification with no visual function or good cosmetic appearance. After discussing the prognosis in detail and explaining the very low expectations of the surgery with the family, we performed a trial for surgery.

The surgical steps included limbal incisions, separation of the iridocorneal apposition with a spatula, formation of the anterior chamber, pupillary reconstruction with the extraction of the pupillary fibrovascular membrane, vitrectomy to clear the hemorrhage, extensive epiretinal membrane peeling to relieve traction on the retina, and laser photocoagulation of the avascular peripheral retina. The eye was left in air. In this case, a presumed diagnosis of familial exudative vitreoretinopathy was made during the surgery.

The same surgery was performed on the fellow eye 10 days later. The surgery resulted in the normalization of IOP in each eye, and the patient maintained ambulatory vision despite the corneal opacities, which improved slightly during the 5-year follow-up.

WATCH IT NOW



Video. Pediatric Bilateral Leukocoria

DISCUSSION

Not every surgical intervention will yield outcomes as favorable as these. But even when the outcome is not as desired, there may still be value in giving a trial for surgery, provided that the eye is not severely microphthalmic, disorganized, or already phthisical. Additionally, pursuing surgical intervention can give the family a sense of satisfaction, knowing that they've tried everything possible to gain vision.

Even when the surgery does not result in significant functional gain, it can still enhance the child's quality of life. For instance, the ability to perceive light is crucial for the diurnal rhythm of hormones, regulation of sleep-wake cycles, and orienting oneself in space and time. Maintaining a cosmetically acceptable globe can also improve the child's self-esteem and reduce bullying. Furthermore, surgery can pave the way for potential restorative technologies in the future.

Thorough counseling and active involvement of the family in the decision-making process are vital parts of this journey. Families might be eager to proceed without being fully aware of realistic outcomes, and surgeons must discuss the goals, risks, and benefits of surgery and set realistic expectations.

Ultimately, when it comes to pediatric retina surgery, surgeons must never give up. With skill, innovation, and perseverance, even the most challenging cases can sometimes have pleasantly surprising outcomes. ■

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WHERE IT ALL BEGAN

Majda Hadziahmetovic, MD, was born in Serbia, where she grew up and finished medical school. She was always scientifically curious and exposed to research from an early age. The research she conducted during her first 2 years of medical school helped her achieve a scholarship to pursue research opportunities in the United States. After 2 wonderful years at Harvard School of Public Health, she knew the United States would be her final destination. Upon finishing medical school, she returned to the United States. While working as a postdoctoral fellow in the lab of Joshua L. Dunaief, MD, PhD, at the University of Pennsylvania, she completed the boards. After a 1-year general surgery internship, she started a residency in Ophthalmology. She went on to a fellowship in medical retina at the Duke Eye Center and then remained as a faculty member. She admits that it was not an easy path, but believes it was the best one for her and made her who she is today.

HER PATH TO RETINA

Dr. Dunaief had the most significant influence on her decision to pursue a clinician-scientist career in ophthalmology. The excitement of new discoveries, as well as writing (and publishing) papers, was inspiring. Also, he had a unique way of transitioning bench-work findings into everyday clinical practice and engaging his patients to be more involved in their own care. Dr. Hadziahmetovic is reminded of his teaching every time she gets a text or an email from a patient sharing new research discoveries with her.

SUPPORT ALONG THE WAY

Professor Tatjana Simic, MD, guided Dr. Hadziahmetovic early in her career, reinforcing that women could be equally (if not more) successful in research than men. At Harvard, Bruce Demple, PhD, welcomed her to the United States for the first time, and she had an incredible 2 years working with him. Dr. Dunaief had the most significant effect on her ophthalmology and retina career; anyone who has met him knows how wonderful of a teacher and mentor he is. Dr. Hadziahmetovic would be remiss not to mention Scott Cousins, MD, at Duke. He encouraged her analytical and critical thinking and a perfectionist view toward science. She has encountered many other amazing people throughout her career who have guided her to be a better person and professional—many of whom are her close friends today.

Dr. Hadziahmetovic's Advice:
Try to thrive in an environment of change and challenge. Do not be afraid to make mistakes, admit that you do not know or cannot do something, and ask for help. Finally, help others whenever you can—that is what medicine is all about.

AN EXPERIENCE TO REMEMBER

There are many situations in which you do something that helps people and improves their lives (or at least you want to believe that is true). That feeling fuels her efforts to be a better clinician, read and learn more, conduct research, and participate in clinical trials. In addition, those moments are a constant reminder to be grateful for your and your family's health. ■

Majda Hadziahmetovic, MD, is a medical retina-trained clinician scientist at Duke Eye Center in Durham, North Carolina. She is involved in patient care, research, teaching, and mentoring.

She is a consultant or on the advisory board for Allergan/AbbVie, Bausch + Lomb, and Protagonist Therapeutics. She can be reached at **majda.hadziahmetovic@duke.edu**.

GLOBAL RETINA CASES: CROATIA

REMOVING EPICILIARY MEMBRANES TO PREVENT PHTHISIS

Hypotony following retinal detachment repair may be addressed with prompt surgical intervention.

BY RATIMIR LAZIC, MD, PHD

Chronic hypotony after successful complex retinal detachment (RD) surgery is a frustrating problem that often leads to irreversible vison loss, phthisis, and corneal opacification in up to 10% of patients.[1] Various nonsurgical and surgical procedures have been proposed to address this problem.[2-4] However, visual and anatomical outcomes have historically been poor.

I hypothesize that earlier detection with improved diagnostics (ie, ultrasound biomicroscopy), use of intraoperative 3D visualization, and bimanual dissection of epiciliary proliferative tissue (which is often the root cause of hypotony after RD surgical repair) has the potential to salvage eyes that are otherwise destined to become phthisical.

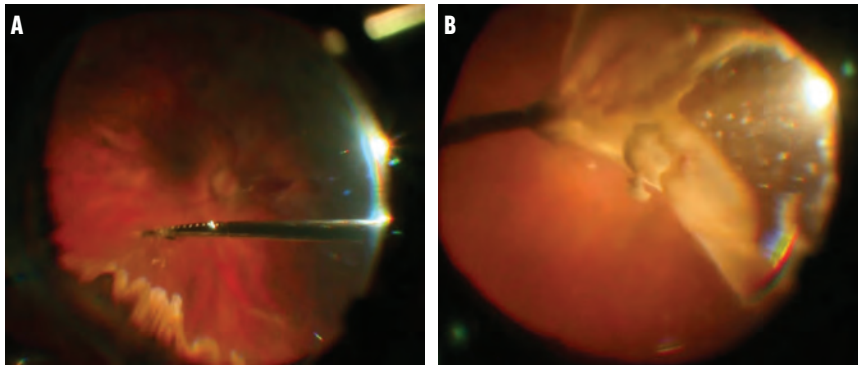


Figure. Removal of epiciliary membranes with serrated forceps under self-indentation with 3D visualization (A). The epiciliary membranes can be extensive, as depicted here (B).

ROLE OF EPICILIARY MEMBRANE

Although there are various reasons why hypotony may arise after RD repair (eg, sclerotomy leaks, cyclodialysis cleft, cyclitic membrane formation), it is presumably caused by chronic traction of the anterior vitreous base on the ciliary body; epiciliary membrane formation and iridociliary adhesion, resulting in low ciliary body detachment; and ciliary body damage and hyposecretion of aqueous humour.

Epiciliary membrane is an unspecified term describing proliferative tissue formation that usually occurs after multiple attempts at RD repair in the setting of proliferative vitreoretinopathy (PVR), where the retina finally reattaches with silicone oil tamponade, but the eye remains hypotonous (IOP < 5 mm Hg). The epiciliary membrane is comprised of various tissues, including vitreous base remnants, anterior retinal flap, PVR membranes in anterior PVR, capsular remnants, and cyclitic membranes, if inflammation is present. Signs of epiciliary membrane growth include decreasing IOP, hyperopic shift, intracameral oil accumulation, and corneal decompensation.

Hypotony in the presence of epiciliary membrane formation is multifactorial, as some degree of rerouting of aqueous outflow is present via areas of bare retinal pigment epithelium after a retinectomy. Postoperative inflammation also reduces aqueous humour production, and mechanical trauma to the ciliary processes after multiple surgical repairs is certainly possible. However, growth of epiciliary membranes, mostly due to proliferation of fibrous tissue, leads to ciliary body detachment, and membranes covering ciliary processes block the release of the humour. Direct destruction of ciliary processes causes irreversible damage to the secretory epithelium.

Prompt detection and surgical intervention is crucial to restore aqueous humour production and increase IOP to potentially revive a percentage of affected eyes.

SURGICAL PROCEDURE

The goals of surgery include the following:

1. releasing traction on the ciliary body, freeing the ciliary processes from compartmentalization to restore aqueous production;
2. freeing the ciliary processes from fibrous tissues that leads to their irreversible functional damage; and
3. lysing the iris-ciliary processes synechiae, which further compromise aqueous production.

I suggest the use of 23-gauge three-port vitrectomy with a chandelier light to allow for a bimanual technique (Video).

If available, intraoperative 3D visualization can enable better illumination and depth of focus. I use the foot-controlled Resight 700 Fundus Viewing System (Carl Zeiss Meditec) to visualize the ciliary body 360°, which appears covered with gray-white membranes. The ciliary processes may also be seen, but in more serious cases, these cannot be identified, as they are entrapped within the membrane complex.

It is crucial to manipulate the membranes gently because the adhesions to underlying tissue can cause choroidal damage. Bleeding must be promptly addressed to reduce the risk of PVR.

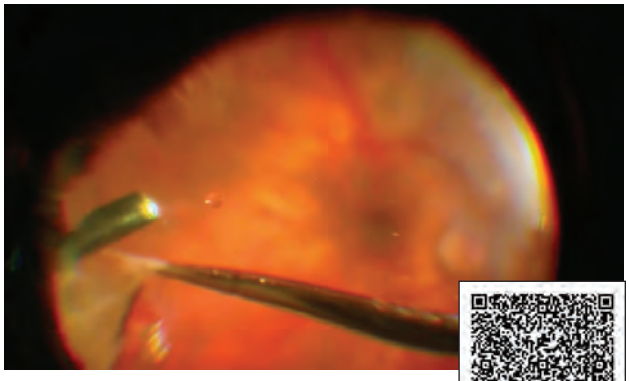
The vitreous base remnants should be meticulously shaved with high-speed, low pulsatile traction (dual blade) cutters with self-indentation. Epiciliary membranes should be removed by carefully pulling and separating them from the ciliary processes with serrated forceps or the vitreous cutter (Figure).

If the membrane conglomerate includes the capsular bag, which is frequently the case, the capsular bag must be removed along with the IOL.

If the anterior retinal flap has not been removed in previous interventions, it must be completely removed at this point, as it contributes to the epiciliary membrane complex formation. In some cases, the lysis of iridociliary synechiae is difficult but must be attempted because the synechiae exert traction on the ciliary body, with consequent ciliary body detachment that covers the ciliary processes, further impairing aqueous humour production.

After epiciliary membrane removal and lysis of iridociliary synechiae, the anatomy of the ciliary body with ciliary processes can be observed, although often reduced in size and number. However, these processes can typically still produce an adequate amount of aqueous humour to restore some level of IOP. Intervening again after the initial improvement of IOP can be beneficial, as new proliferative tissue may emerge.

WATCH IT NOW



Video. Surgical Removal of Epiciliary Membrane

This novel surgical approach, in my experience, results in a 3- to 5-mm Hg increase in IOP, which can suffice to raise IOP to higher than 8 mm Hg for approximately one-third of eyes. Another one-third remain hypotonous with IOP between 3 mm Hg and 5 mm Hg, which can still prolong the eye's viability and volume with some ambulatory vision. The remaining one-third will likely progress to phthisis, despite intervention. Similar outcomes have been reported, in which the lysis of adhesion between the iris and the ciliary body and its processes, as well as removal of lens remnants and other fibrocellular tissue, resulted in a final postoperative IOP increase of up to 15 mm Hg.[4,5]

PREVENTING EPICILIARY MEMBRANE FORMATION

Meticulous vitreous base shaving with self-indentation and 3D visualization, anterior retinal flap removal after retinectomy, meticulous removal of any bleeding, and strong antiinflammatory postoperative therapy (such as administration of intraocular methotrexate) is the best prevention against epiciliary membrane formation.

If the membrane does form, early detection is based on signs of low IOP in silicone oil-filled eyes, pupillary membranes, pupil dilatation, oil in the anterior chamber, and corneal decompensation. Radical dissection as described above can result in salvaging some eyes from progressing to phthisis, although visual outcomes in such cases usually do not show significant improvement.

WORTHWHILE TO TRY

Even with restoration of aqueous humour production and subsequent modest improvement in IOP, reduced aqueous humour production may persist due to irreversible damage to secretory ciliary processes function.

Despite the low reported success rates of such interventions by a number of authors,[1,4,5] today's improved capabilities of early detection, 3D intraoperative visualization, and improved instrumentation/surgical techniques make epiciliary membrane removal worth undertaking to attempt to preserve visual and anatomical function. ■

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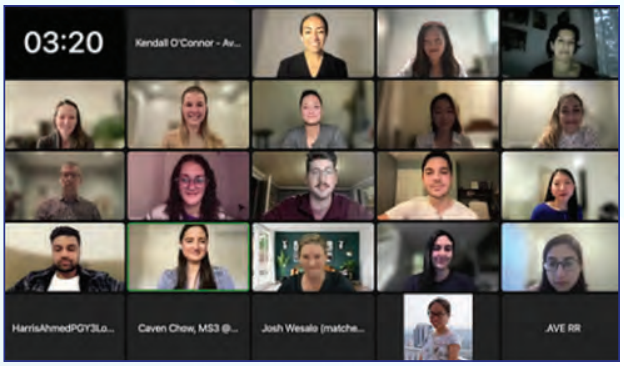
EXPLORING PATHWAYS IN OPHTHALMOLOGY

Geeta Lalwani, MD; Margaret Chang, MD; Alan Ruby, MD; Jay Sridhar, MD

Identifying the right practice setting can be an arduous task. In a recent YoungMD Connect workshop, Geeta Lalwani, MD; Margaret Chang, MD; Alan Ruby, MD; and Jay Sridhar, MD, discussed a range of setups—including group practice, solo practice, and academia—and shed light on how private equity (PE) factors into the equation.



THE PROS AND CONS OF WORKING IN A PRIVATE PRACTICE

Geeta Lalwani, MD | Boulder, CO

"Lifestyle is important to one's happiness."

Dr. Lalwani emphasized the importance of factoring lifestyle and location into your practice considerations. For example, do you need to be near family, or close to the mountains or beach? Talking to longtime practitioners can help you to understand what type of practice will suit you. With any practice you target, research the culture as thoroughly as possible, she advised.

Dr. Lalwani also provided some sample questions to ask when interviewing for a private practice position, including:

1. What does it take to become a partner?
2. How would I build equity within the practice?
3. What is the practice's parental leave policy?

CANDID TALK ABOUT PE MEDICAL PRACTICES

Alan Ruby, MD | Royal Oak, MI

"If you like the people running a practice, you'll set yourself up for success."

Shedding more light on PE, Dr. Ruby described how PE medical practices are just private practices that have partnered with a PE enterprise. PE firms choose practices that are well-run, and they do not want to interfere with that success. PE is run like a business, wherein certain financial risks may be magnified or minimized.

Rather than limiting your options to exclusively PE or private practice, Dr. Ruby suggested evaluating the practice itself. Leverage your negotiation power, he advised, as private practices, PE practices, and academic institutions all compete for high-quality people. Focus on a subspecialty that sets you apart from other candidates. As for research, Dr. Ruby noted that, regardless of affiliation, most enterprises do not limit research opportunities.

WHAT YOU NEED TO KNOW ABOUT PE

Margaret Chang, MD | Sacramento, CA

"Not all PE is the same. How these practices are structured and run differs."

As Dr. Chang noted, the structure of PE practices differs based on their vertical versus horizontal integration. Vertically integrated PE practices are often in the same local area and refer to each other. They usually combine optometry, general ophthalmology, and retina. An example of a horizontally integrated group is a large organization of retina-only practices in different geographic areas. They share decisions on equipment, drug purchases, and clinical research.

Dr. Chang commented that in PE, the structure of the partnership is often different than it is in private practice. Although the ending partnership salary may not be as high as in traditional private practice, the associate salary is often much higher, and the track to partnership is usually much shorter. There is no buy-in at the end of the associate track, and there is usually some profits interest or equity based on the growth of the parent company that may be offered at the end of the associate track. Dr. Chang added that, in a PE setting, the amount of physician versus corporate control may vary.

WHAT YOU NEED TO KNOW ABOUT WORKING IN ACADEMIA

Jay Sridhar, MD | Miami, FL

"Take all advice with a grain of salt, because everyone's employment needs are different."

On the academic side, Dr. Sridhar discussed some of the strengths and drawbacks of this practice setting. In academia, there is less volatility related to market forces, such as contractions (like during the COVID-19 pandemic). It is also easy to practice multidisciplinary care, as hospitals provide the time, resources, and access to specialists. It is more challenging to coordinate collaborative care in private practice.

As for the drawbacks, Dr. Sridhar described some of the operational inefficiencies associated with academic practice. For example, the workflow will not be as fast as in private practice, and physicians may not get the accountability or resources they need. He also noted that there is great access to research in an academic setting, but also more bureaucracy (plus, pharmaceutical trials are more difficult to conduct in academia). Further, academic institutions make money through grant funding or by clinicians generating revenue, so practitioners may need to justify their salaries.

CONCLUSION: There is no one-size-fits-all practice setting. Understanding the differences between the various options will help young ophthalmologists to identify the path that appeals most to them professionally and personally, and to set out—and occasionally pivot—with confidence.

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Eleonora Lad, MD, PhD, and Ramin Tadayoni, MD, PhD

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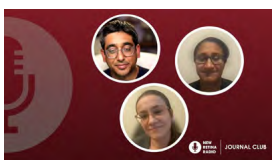
Lediana Goduni, MD, and Prethy Rao, MD, MPH



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GLOBAL RETINA CASES: MEXICO

BRAO ASSOCIATED WITH PREPAPILLARY VASCULAR LOOP

Systemic workup may be warranted to rule out a more serious condition.

BY CARLOS VARGAS RIAÑO, MD; HEBER GARAGARZA MARISCAL, MD; JANS FROMOW GUERRA, MD, PHD, MSC; JUAN MANUEL JIMENEZ SIERRA, MD; AND OCTAVIO TURCIO ACEVES, MD

Prepapillary vascular loop is a congenital retinal anomaly of either the arterial or the venous system.[1] The embryonic origin of this condition is uncertain but is believed to be derived from the 100-mm stage of mesenchymal cells that originate in the papilla to vascularize the retina. These vessels project from the optic disc into the vitreous cavity and then return to vascularize the retina with no connection to the hyaloid artery.[2] It is usually an asymptomatic, unilateral finding detected on routine examination, but 9% to 17% of cases are bilateral.[3]

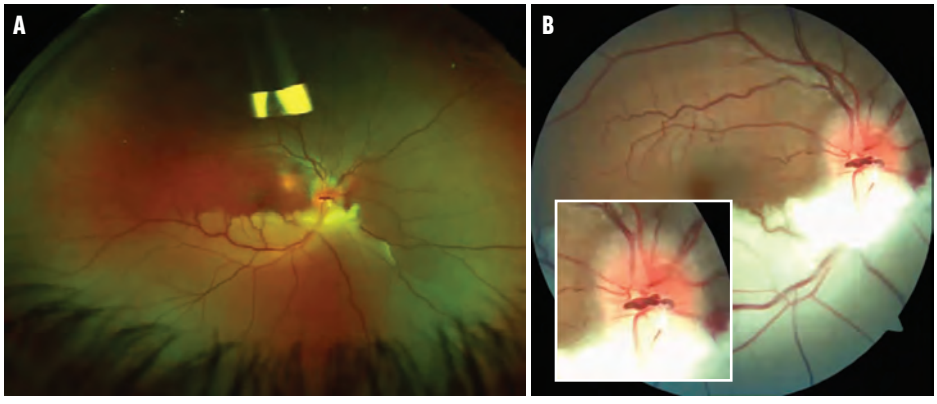

Figure 1. Ultra-widefield photography of the right eye showed an optic disc with blurred borders, a prepapillary vascular loop, and significant pallor due to edema of the inner layers of the macula and inferior retina that respects the fovea (A). A 45° photograph highlights the retinal pallor and fovea (B).

The incidence of prepapillary vascular loop is approximately 1 in 9,000 patients. Symptoms can include sudden vision loss, vitreous hemorrhage, amaurosis fugax episodes, and/or scotoma associated with branch retinal artery occlusion (BRAO).[3,4]

Here we discuss the case of a patient who presented with a sudden scotoma in the upper visual field. An inferior BRAO was detected that was associated with a prepapillary vascular loop.

CASE REPORT

A healthy 37-year-old woman presented to the clinic complaining of sudden scotoma in her upper visual field for the last 24 hours. The patient denied any significant medical, surgical, or family history and reported no smoking, use of oral contraceptives, or trauma. An ophthalmic examination revealed a BCVA of 20/30 OU with no significant refractive error. The anterior segment examination of each eye was unremarkable, and IOP was 15 mm Hg OU.

Dilated fundoscopy of the left eye was normal. The right eye showed a type IV prepapillary vascular loop on ultra-widefield photography, according to the Mansour et al classification of the inferior retinal branch artery (Figure 1).[5] Ultra-widefield fundus autofluorescence of the right eye revealed an area of inferior parapapillary hypoautofluorescence corresponding to the area of increased retinal edema, along with another, smaller area of hypoautofluorescence corresponding to a parapapillary hemorrhage (Figure 2).

Fluorescein angiography revealed hypofluorescence due to the absence of filling of the vascular prepapillary loop and inferior temporal artery (Figure 3). Macular OCT showed

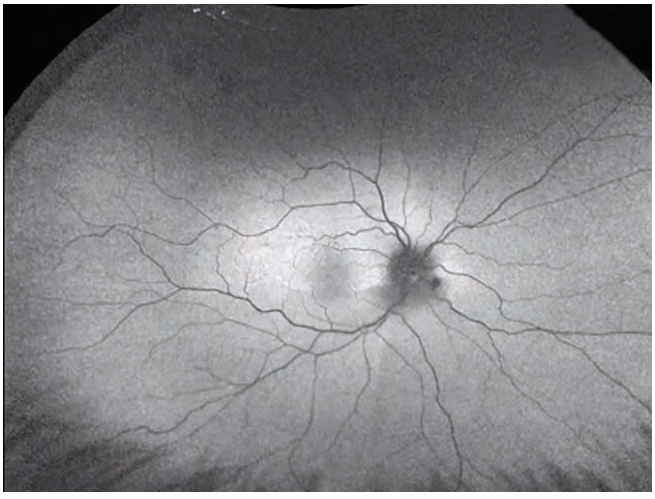

Figure 2. Ultra-widefield fundus autofluorescence showed hypoautofluorescence corresponding to the area of increased retinal edema and a smaller area of hypoautofluorescence corresponding to a parapapillary hemorrhage.

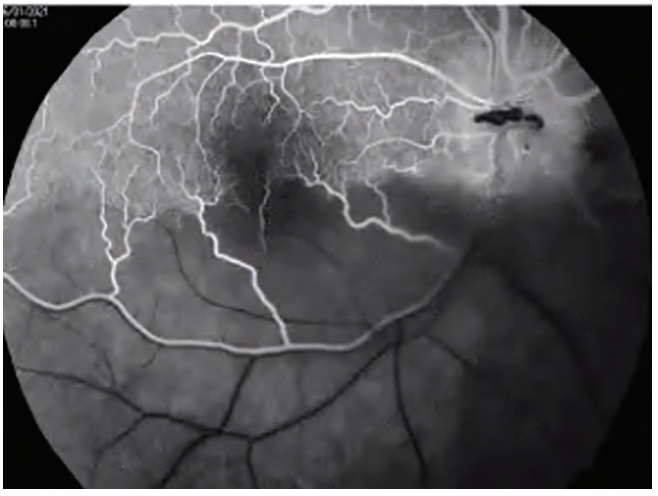

Figure 3. Fluorescein angiography of the arteriovenous phase showed filling of the superior arteries and hypofluorescence due to the absence of filling of the vascular loop and inferior arteries.

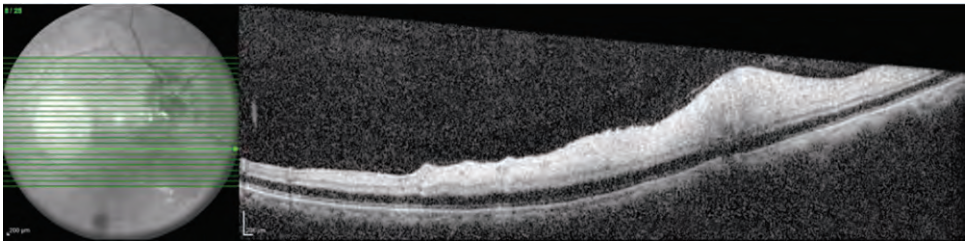

Figure 4. OCT showed hyperreflectivity of the internal layers in the area of the inferior macula due to edema secondary to ischemia that does not allow for delimitation of the cellular layers.

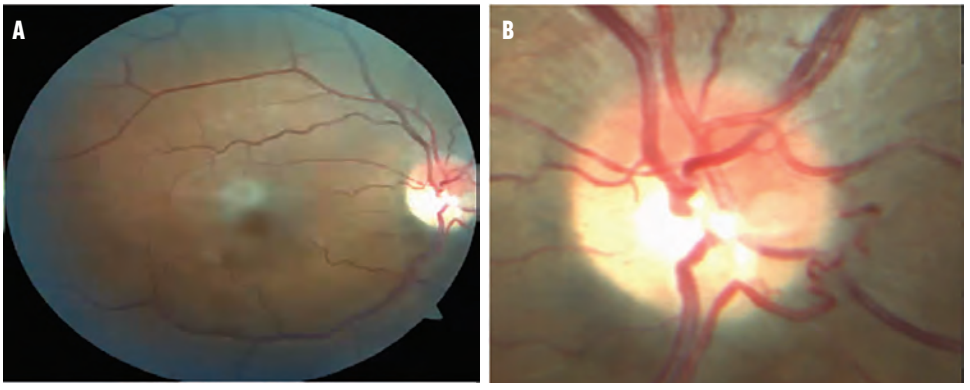

Figure 5. After 3 months of follow-up, the fundus photographs show reperfusion of the inferior temporal area (A) and uncoiling of the vascular loop, as well as some degree of reperfusion of the affected lower vessel (B).

hyperreflectivity of the internal retinal layers in the area of the inferior macula due to edema secondary to ischemia (Figure 4).

FURTHER TESTING

Given the young age at presentation with no relevant history, systemic testing was performed, including a complete blood count, basic metabolic panel, c-reactive protein, erythrocyte sedimentation rate, HIV serologic test, venereal disease research laboratory, fluorescent treponemal antibody-absorption, purified protein derivative, antinuclear antibodies, and antiphospholipid antibodies—all of which came back negative or within normal range. A cardiology referral was also made to help rule out a systemic condition, which showed normal results.

A diagnosis of BRAO associated with a prepapillary vascular loop was made with a recommendation to monitor the patient without further treatment due to adequate visual acuity. Fundus photography showed changes during the 3-month follow-up period, including reperfusion of the inferior temporal area and uncoiling of the vascular loop (Figure 5). BCVA remained 20/30 OU.

MECHANISM OF OCCLUSION

BRAO secondary to a prepapillary vascular loop has an incidence of 4%,[2] occurring most frequently in the lower vessels. Several mechanisms have been described to explain the development of occlusion in certain patients, including loop twisting, thrombosis, vitreous traction, trauma, or a combination of these factors.[6] However, the most widely accepted theory is that hemodynamic turbulence within the vascular loop produces mechanical endothelial damage, resulting in the formation of an intraarterial clot and ultimately leading to an arterial or vein occlusion.[7] Over

time, the absence of blood flow leads to the collapse of the arterial walls, and the vascular loop is replaced by glial tissue.

BE WARY OF COMPLICATIONS

In the present case, the vascular loop disappeared over time. Although the exact mechanism of BRAO and uncoiling of the prepapillary vascular loop remains unclear, careful observation and monitoring of patients with a prepapillary vascular loop is crucial due to the potential for serious complications, such as vitreous hemorrhage, BRAO, and macroaneurysm rupture. It is also important to perform thorough testing in young patients to rule out systemic conditions associated with BRAO. ■

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AVOID COMMON RETINA TESTING PITFALLS

A breakdown of five diagnostic challenges and how to avoid them.

BY JOY WOODKE, COE, OCS, OCSR

Diagnostic testing services are essential to retina practices. However, high usage of diagnostic testing can prompt payer scrutiny and requires correct coding and proper documentation. One way to identify shortcomings and provide improvement opportunities is by conducting frequent internal reviews. To help with these reviews, let's take a close look at five common pitfalls to watch out for.

NO. 1: MISSING PHYSICIAN ORDER

After comprehensive error rate testing chart reviews, the Medicare administrative contractor (MAC) Wisconsin Physician Service reported that the majority of the deficiencies prompting audit failures and causing claim denials was a missing physician order.[1] Anecdotally, AAO consultants who provide external chart audits also found this absence to be the most common deficiency.

A physician order must be documented for all delegated testing services. This should include information detailing the tests being ordered, which eye is being tested, and the reason for the tests. New patients must be examined to establish the indication for the test. Standing orders and screening tests are not payable by any payer, even if pathology is found.

For established patients, the order for delegated tests is often documented on the previous encounter. This should be included in the chart notes provided during an audit.

Some electronic health record (EHR) vendors have the functionality to capture this crucial documentation. Others do not provide this in the standard templates. Furthermore, some vendors provide the ability to enter the physician order into the EHR, but it is not included in the printed chart note. No matter who your EHR vendor is, it is important to confirm that this crucial component of the medical record is captured.

NO. 2: MEDICAL NECESSITY PER PAYER

Payer policies vary, and they often have specific coverage requirements and definitions for medical necessity. For example, the MAC Palmetto GBA has published local coverage determination (LCD) L34426, which provides guidance for fluorescein angiography (FA) and ICG angiography (ICGA).[2] In the policy, ICGA has specific medical necessity requirements, which can be reported as current procedural terminology (CPT) code 92240 and, when provided with FA, as CPT code 92242.

This policy states that performing both tests may be a valuable evaluation for the following conditions:

- retinal neovascularization,
- choroidal neovascularization,
- serous detachment of the retinal pigment epithelium (RPE),
- hemorrhagic detachment of the RPE, and
- retinal hemorrhage.

When ICGA is ordered, the Palmetto GBA LCD L34426 guidance states that chart documentation should include one of the following:

- evidence of ill-defined subretinal neovascular membrane or suspicious membrane on previous FA,
- the RPE does not show subretinal neovascular membrane on current FA, or
- presence of subretinal hemorrhage or hemorrhagic RPE. An FA need not have been done previously.

The local coverage article (LCA) A56774 published by

CODING QUICK LINKS


Retina Coding: Complete Reference Guide


Local Coverage Determination Policies


Practice Management Resources for Retina

Palmetto GBA provides the covered ICD-10-CM codes that support medical necessity for CPT codes 92235 for FA, 92240 for ICGA, and 92242 when combined.[2]

NO. 3: EXCEEDING FREQUENCY LIMITATIONS

Another common deficiency that can prompt audit failures and cause claim denials is exceeding outlined frequency limits.

For example, fundus photography (CPT code 92250), has frequency limitations published in many payer policies. The Medicare MACs Cigna Government Services (in LCA A57071) and National Government Services (in LCA A56726) both indicate that fundus photography is "usually medically necessary no more than two times per year."[2] Aetna, in its policy 0539, states that fundus photography provided more than twice a year would require chart documentation justifying medical necessity.[3]

OCT also has frequency limits in some payer policies. For example, WPS is one of six MACs with a policy for scanning computerized ophthalmic diagnostic imaging, or OCT. LCD L34760 limits OCT to every 2 months when managing retinal disease and monthly for patients treated with intravitreal injections.[2] Novitas has similar language in its LCD L35038 and defines monthly as every 28 days in LCA A57600.[2]

Noridian does not have a published policy for OCT but references frequency of use in its bevacizumab (Avastin, Genentech/Roche) LCAs for both jurisdiction E (A53008) and jurisdiction F (A53009).[2] It confirms the use of OCT to monitor and evaluate the need for additional intravitreal injections of bevacizumab every 4 to 6 weeks.

To avoid denials due to frequency limitations, review your payer policies to confirm their unique guidance.

NO. 4: INAPPROPRIATE UNBUNDLING

When multiple testing services are performed on the same day, National Correct Coding Initiative edits should be reviewed to identify if any of the services are considered bundled. If so, the CPT codes will either have an indicator defined as either 0, mutually exclusive, or 1, comprehensive.

Mutually exclusive edits identify services that are bundled and can never be unbundled with the modifier –59, distinct procedural service. When two tests are considered mutually exclusive (eg, CPT code 92134, OCT, posterior segment, and 92133), providers should bill for the test that contributes most to the treatment plan on the day of the encounter. Recovery auditors are monitoring for inappropriate unbundling of mutually exclusive testing services and can automatically recoup based on claims data.

When two tests are bundled with an indicator of 1, comprehensive, there may be circumstances where providers can unbundle. For retina testing services that are inherently bilateral, it's important to confirm published payer policies for appropriate scenarios. For example, CPT code 92134, OCT, posterior segment, and 92250, fundus photography, are bundled as comprehensive. To then unbundle with modifier –59, the tests must be distinct services.

In its LCD L35038, Novitas outlines that these tests may be performed on the same day when "necessary to evaluate and treat the patient" and should include documentation of the medical necessity.[2] The guidance continues that frequently unbundling these tests may "trigger focused medical review."

Two separate indications for the two tests (eg, fundus photography for a choroidal nevus and OCT for diabetic macular edema) would meet this payer's requirement.

NO. 5: WRONG PAYER'S RULE

Payer policies may vary, so using one payer's policy or perceived rules as guidance for another insurance carrier's claims may cause denials or prompt reviews. Although it is time consuming, it is necessary to research and review specific payer policies to confirm coverage, frequency limitations, and medical necessity definitions for the services provided.

Providers can start with a comprehensive review of local MAC policies and then confirm Medicare Advantage, commercial, and Medicaid guidelines. It is essential to communicate these nuances with the entire practice team.

Implementing frequent internal reviews and watching out for these deficiencies can help you avoid audit failures and claim denials. For more coding tips, common pitfalls to avoid, and policy outlines, check out the *Coding Quick Links*. ■

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FIGURE 2

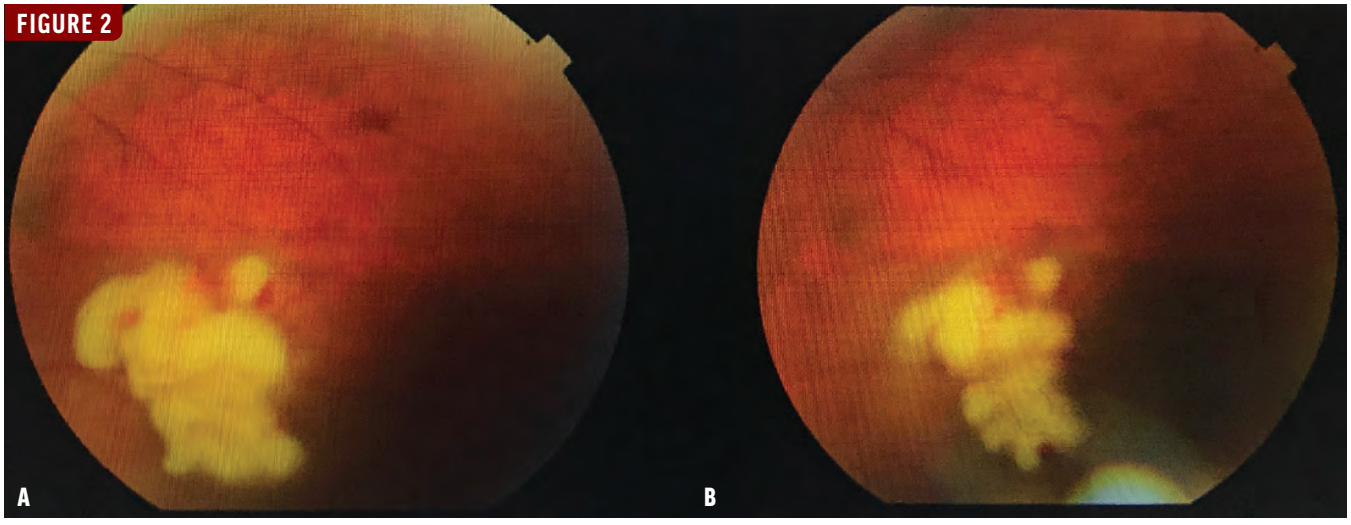
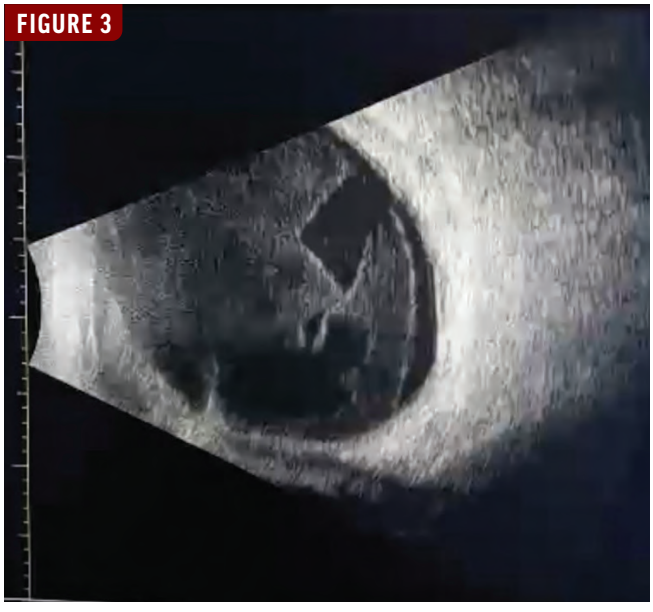


FIGURE 3



(Continued from page 58)

fundus examination of his left eye revealed a flat, white, creamy intraretinal lesion with satellite lesions with no overlying vitreous debris (Figure 2A). B-scan ultrasonography of the right eye revealed diffuse heterogeneous, fibrinous, septated vitreous debris (Figure 3).

At this time, we suspected fungal endophthalmitis in the right eye and fungal chorioretinitis in the left eye but could not rule out bacterial etiologies. The patient was advised to stop the immunosuppressants and was placed on intravenous voriconazole, amphotericin B, and cefepime and was admitted to the hospital for further workup. Three rounds of anterior chamber paracentesis and four intravitreal injections of antibiotics and voriconazole were administered in each eye, but no organisms grew in culture (Figure 2B, left eye). A limited core pars plana vitrectomy with vitreous biopsy was ultimately performed in the right eye, which grew mold that speciated to *S. apiospermum*.

The patient was then placed on oral voriconazole, and over the next month, five rounds of intravitreal voriconazole were administered in each eye. The right eye progressed to no light perception despite treatment. Further intravitreal injections were deferred in his right eye to prioritize preserving visual acuity in his left eye, which experienced mild improvement in the size of the intraretinal lesion. ■

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Note: Photos should be 400 dpi or higher and at least 10 inches wide.

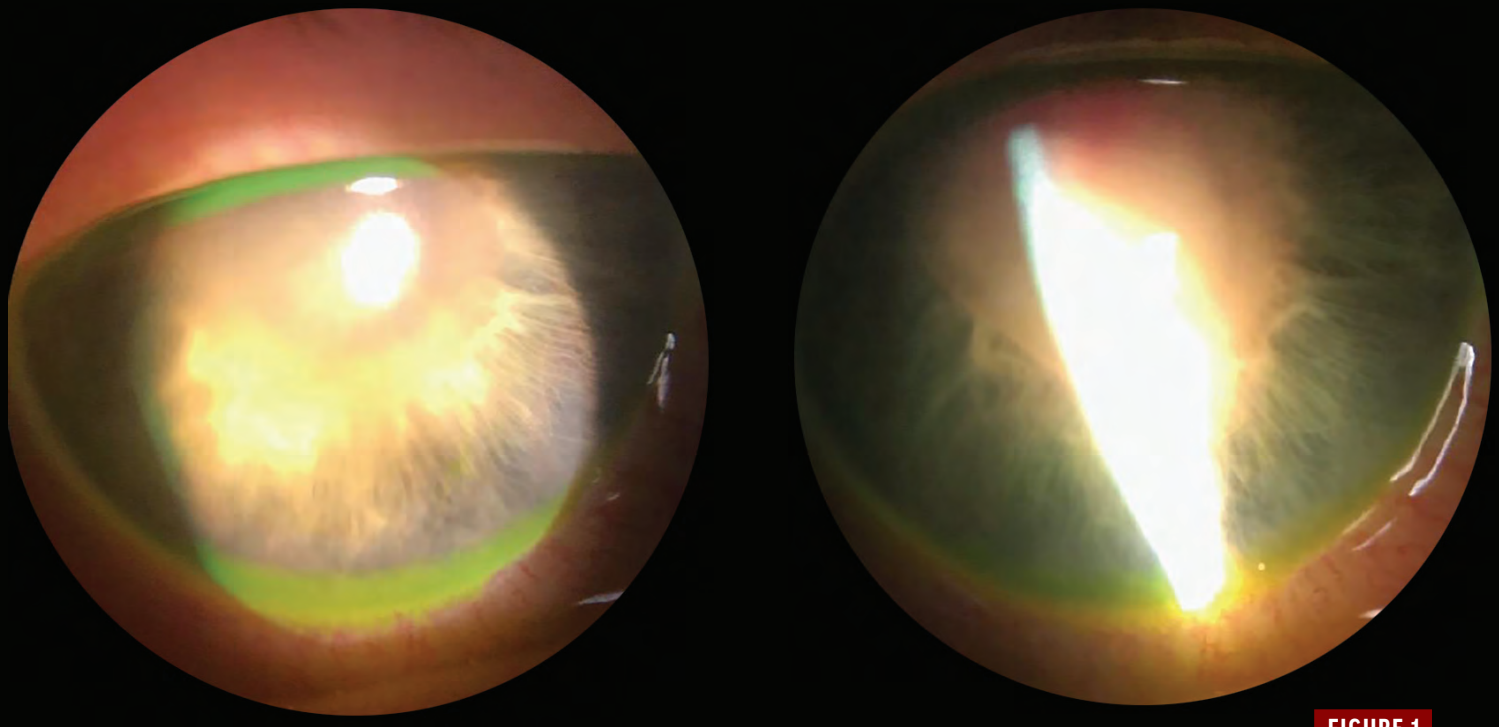

FIGURE 1

OCULAR INFECTION WITH *SCEDOSPORIOSIS APIOSPERMUM*

This chorioretinal infection was responsive to combination intravitreal and systemic antifungal therapy.

BY DYLAN SADOWSKY, MD; JUSTIN SHORTELL, MD; AND RYAN LEITE, MD

Scedosporiosis apiospermum is a mold often found in polluted water that can cause several types of infections in humans, with immunocompromised patients being the most susceptible.[1,2] Potential ocular infections associated with *S. apiospermum* include keratitis, chorioretinitis, and endophthalmitis.[3]

THE CASE

A 57-year-old White man who was on chronic immunosuppression presented to our ophthalmology clinic with right eye pain, redness, and visual changes 1 month after a liver transplant. One week prior, his optometrist had difficulty visualizing his optic nerve and observed an "internal filminess," for which he was prescribed oral NSAIDs and erythromycin ointment and was advised to follow up with an ophthalmologist. Additional ocular symptoms included photophobia, blurred vision, floaters, and mild swelling of his right eye.

The patient's initial VA was hand motion OD and 20/40 PH 20/25+ OS. His IOP, pupils, and extraocular muscles were within normal limits in each eye. His right eye was noted to have 1+ conjunctival injection, 4+ anterior chamber cell, and flare with a dense yellow-brown material protruding from the posterior chamber into the anterior chamber, limiting the view of the retina (Figure 1). A dilated

(Continued on page 57)

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Ocular or Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Neovascular AMD

In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

Intraocular Inflammation

In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.

Increased Intraocular Pressure

Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

Clinical Trials Experience

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

A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

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

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye

Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization

Punctate keratitis included: punctate keratitis, keratitis

Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.

Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.

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

Lactation

Risk Summary

It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.

Females and Males of Reproductive Potential

Contraception

Females: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.

Pediatric Use

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

Geriatric Use

In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing neovascular AMD, endophthalmitis, and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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

SYF-PI-17Feb2023-1.0

2/23 US-PEGGA-2200163 v2.0

NOW APPROVED: the first and only FDA-approved treatment for GA secondary to AMD[1]

GA unravels so much
SAVE RETINAL TISSUE BY SLOWING PROGRESSION[1-3]

SYFOVRE achieved continuous reductions in mean lesion growth rate* vs sham pooled from baseline to Month 24[1]

Monthly	Every Other Month (EOM)
OAKS trial (mm^2): (3.11 vs 3.98) **22%**	OAKS trial (mm^2): (3.26 vs 3.98) **18%**
DERBY trial (mm^2): (3.28 vs 4.00) **18%**	DERBY trial (mm^2): (3.31 vs 4.00) **17%**

SE in trials (monthly, EOM, sham pooled): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]
Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]

AMD=age-related macular degeneration; GA=geographic atrophy; SE=standard error.

Learn more about the SYFOVRE clinical data at SyfovreECP.com/efficacy

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24-month, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026–1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338–345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

Apellis

SYFOVRE™
(pegcetacoplan injection)
15 mg / 0.1 mL