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Retina Today

MARCH 2024 VOL. 19, NO. 2
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Diversity *and* Inclusion

The state of affairs and what the future holds.

eyetube

HEALTH DISPARITIES IN THE REAL WORLD: LESSONS FROM AI

A NEW PERSPECTIVE ON THE RETINA WAGE GAP

AN INTERVIEW WITH JULIA A. HALLER, MD

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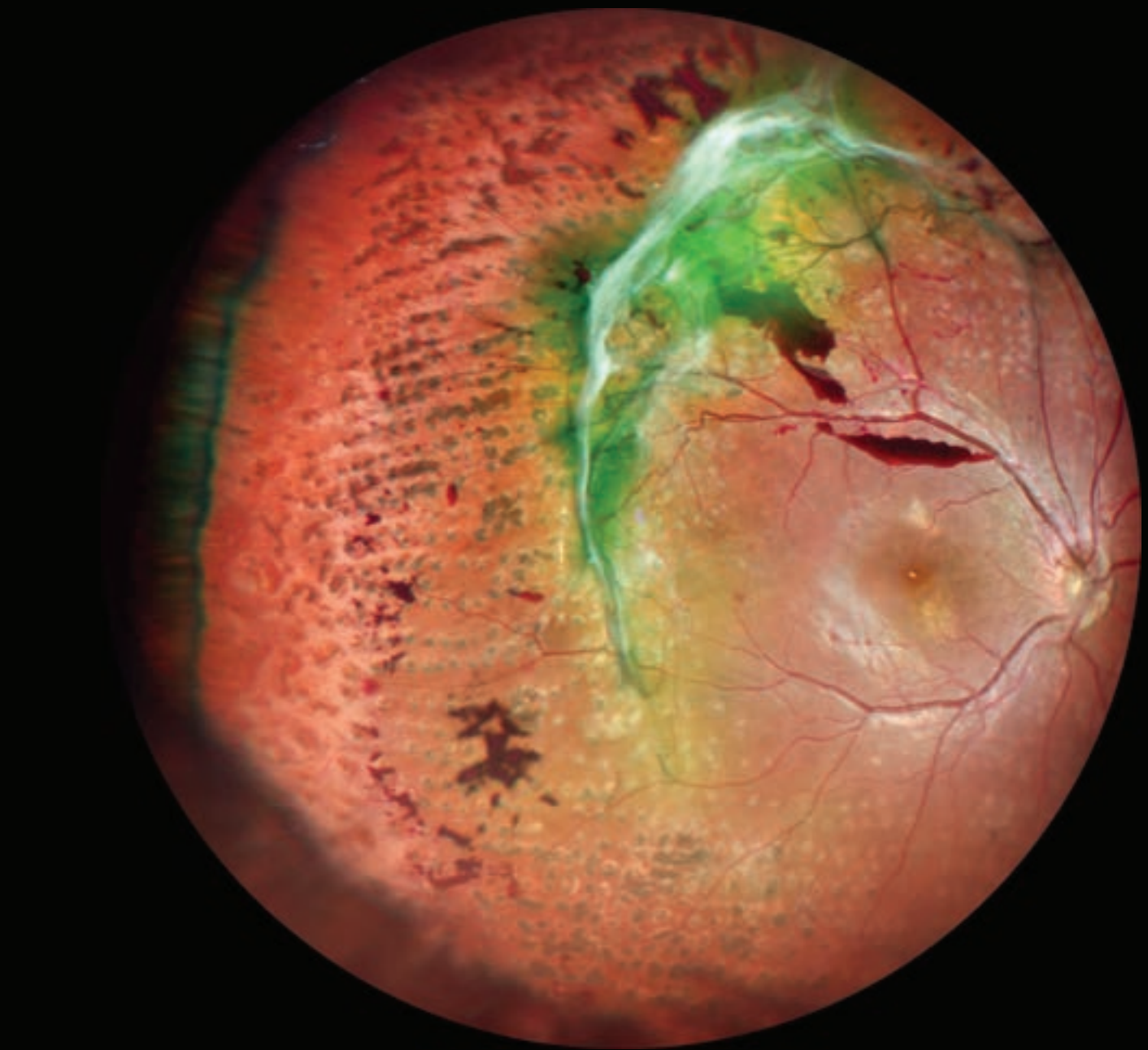
DIABETIC RETINOPATHY:

20/25, for How Long?



The 4th Annual NIDEK IMAGE OF THE YEAR

Figure 1. A Mirante 163** ultra-widefield color image of a right eye with diabetic retinopathy taken from the temporal position when the patient presented in early 2023. The image shows fibrovascular traction in the near periphery, temporally, and superiorly, and a subhyaloid hemorrhage. Laser scars are also visible for 360˚.

IMAGE OF THE YEAR

BY MARLON RAFAEL GARCÍA ROA, MD

Marlon Rafael García Roa, MD, of the Instituto Mexicano de Oftalmologia, is the recipient of the 4th Annual NIDEK IMAGE OF THE YEAR Award. His case of a 25-year-old patient with diabetic retinopathy and macular atrophy in the right eye (Figure 1) highlights the imaging capabilities of the Mirante Scanning Laser Ophthalmoscope (NIDEK).

A 25-year-old female patient presented to our clinic at the Instituto Mexicano de Oftalmología I.A.P. (Santiago de Querétero, Mexico) in early 2023 with diabetic retinopathy in the right eye (Figure 1) and macular atrophy in the left eye (Figure 2). She had undergone surgery 1 year prior for tractional retinal detachment in the left eye, after which the vision was counting fingers at 30 cm.

My team and I used the Mirante to capture multimodal imaging of the right eye, including ultra-widefield color images and green fundus autofluorescence (FAF). These showed fibrovascular proliferation in the temporal periphery. Also present was a subhyaloid hemorrhage in the posterior pole (Figure 1), and because this configuration increases the risk of acute contraction (the so-called "crunch") after anti-VEGF injections or laser treatment, these interventions must be used cautiously. Her vision was 20/25 BCVA in the right eye. We decided to treat this eye with vitrectomy with silicone oil, after which her vision stabilized at 20/60 UCVA for 2 to 3 months.

FOLLOW-UP

My team and I saw this patient for a follow-up visit in December 2023. Her postoperative visual acuity in the right eye was 20/40 UCVA and 20/25 BCVA. The eye appeared stable following the vitrectomy (Figures 3–5). We plan to extract the silicone oil in February 2024. The left eye's acuity remained counting fingers at 30 cm. Using the Mirante OCT, we saw disorganization of the retina's inner layers and external lines lost (not shown), so we decided not to operate further on this eye. We will closely monitor the patient with Mirante imaging going forward.

CLINICAL BENEFITS OF THE MIRANTE

Because there is a high rate of uncontrolled diabetes among the citizens of Mexico, even in young people, diabetic retinopathy is common in our patient population. We receive many referral cases at our institute because of our retina fellowship program. The various imaging modalities on the Mirante have proven very useful in evaluating both adults and children—in particular, these applications help us diagnose retinopathy of prematurity and peripheral retinal diseases. We use the Mirante for diagnosis and treatment decisions, as well as follow-up.

We have had the Mirante device for approximately 2 years; it was our first widefield imaging system. We use it in approximately 50% of our patients, and our most common applications are the green FAF and Retro mode for pathologies such as macular degeneration and central serous retinopathy. We use the color ultra-widefield SLO images for retinal detachments and other traumas. Our patients also appreciate the images the Mirante produces; seeing a visual of a lesion or detachment helps them and their loved ones understand what is happening to their vision. ■

MARLON RAFAEL GARCÍA ROA, MD
- Instituto Mexicano de Oftalmología I.A.P., Santiago de Querétaro, Mexico
- drmgroa@hotmail.com
- Financial disclosure: Consultant and/or lecture fees (Alcon, NIDEK)

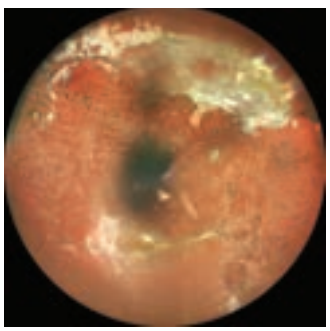


Figure 2. A Mirante 163°* ultra-widefield color image of the patient's left eye taken in January 2023 showed a fibrovascular proliferation in the superior far periphery, as well as a remanent of proliferation with perifoveal traction.

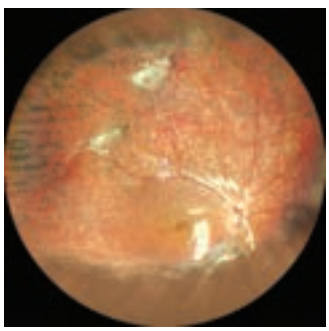


Figure 3. A Mirante 163°* ultra-widefield color image of the posterior pole of the patient's right eye after undergoing vitrectomy showed no fibrovascular traction in the near periphery.

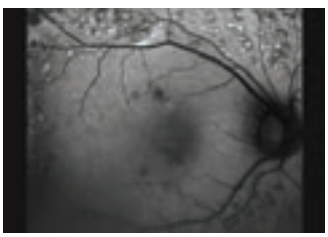


Figure 4. A Mirante 89°* green fundus autofluorescence (FAF) image of the patient's right eye after undergoing vitrectomy with retained silicone oil reveals points of hypo-fluorescence in the perifoveal area superiorly and inferiorly, indicative of microhemorrhages. Outside the temporal vascular arcades, there are points of hyper-fluorescent spots surrounded by hypo-fluorescence that indicate areas where laser marks were made during a previous surgery.

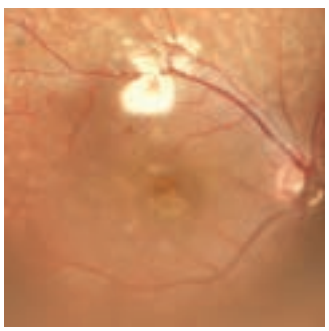


Figure 5. A Mirante 89°* color image of the right eye with the silicone oil evident in the perifoveal area (bright spots). The author and his team will remove the silicone oil at a later visit.

*Measured from the center of the eye.

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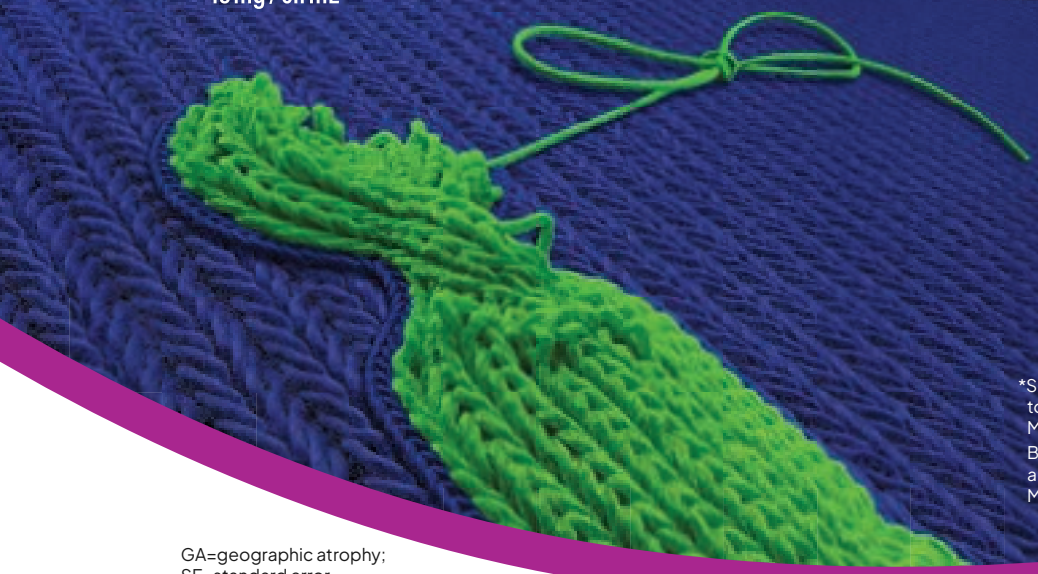
SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL



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[1,4]

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]

GA=geographic atrophy;
SE=standard error.

Explore the long-term data

The CMS-assigned permanent J-code for SYFOVRE is J2781—effective 10/1/23[1]

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

ADVERSE REACTIONS

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

PATIENT COUNSELING INFORMATION

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

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

SYF-PI-30NOV2023-2.0

12/23 US-PEGGA-2200163 v4.0

ALL HANDS ON DECK


"Doc, I can't lose my eyesight." "I need to be able to see!" "Oh, my eyes are very important to me."

As retina specialists, we regularly hear some version of these statements from our patients. Americans across all racial and ethnic backgrounds cite loss of vision and blindness as the most feared health outcome.[1] One of the most gratifying aspects of caring for patients with complex retinal diseases is helping them maintain and, in many cases, improve their vision. One of the most heartbreaking aspects is knowing that some face permanent visual impairment—for example, young patients with bilateral tractional retinal detachments from proliferative diabetic retinopathy. Vision loss brings loss of independence, loss of the ability to provide and care for family and oneself, and diminished quality of life.[1] With our incredible advances in ophthalmology and innovations in retinal care, why are Americans losing vision from treatable conditions like proliferative diabetic retinopathy?

Disparities in vision outcomes across racial and ethnic patient groups are well-known.[2,3] How can we address these disparities to ensure that patients from all backgrounds are achieving their best vision health? Many clinical trials to date have limited demographic data on race and ethnicity, and retina clinical trial participants have not reflected the genetic and geographic heterogeneity of the US population. (Sexual orientation still isn't collected, for the most part. For more on this topic, see *Further Reading*). Additionally, ophthalmology remains among the least diverse specialties.[4] Fortunately, the number of women entering medicine and ophthalmology is increasing. Still, we have yet to understand why female academic ophthalmologists are paid less than their male counterparts,[5] and why there are relatively few female department chairs and women in leadership roles.

In this issue, we will examine some of these topics. We spoke with Julia A. Haller, MD, about her own inspirational *JAMA* editorial, "Cherchez la Femme," from 2015 (see the featured article *Diversity in Retina Leadership: Where are the Women Now?*).[6] Dr. Haller noted that Neil M. Bressler, MD, editor-in-chief of *JAMA Ophthalmology*, had invited her to write that piece and that much of the increased diversity at *JAMA* is thanks to his overt efforts to increase the number of female editorialists.

Also in this issue, Ron Adelman, MD, MPH, MBA, tackles gender differences in Medicare payment among retina specialists (see the featured article *A New Perspective on the Retina Wage Gap*). His team studied physicians' total annual payment through Medicare in 2020 and found that female retina specialists received 65 cents on the dollar compared with their male counterparts.[7] When they controlled for the number of patients seen, the disparity lessened to 89 cents on the dollar. The ensuing panel discussion and audience participation circled around the many potential underlying causes for the disparity, one of which being that women might under-code clinic visits. Jeffrey S. Heier, MD, closed out the session by pointing out that it's perhaps more likely that men over-code their visits. It's such a small distinction, but the room seemed to shift as the implication struck home. Many of us have thought more carefully about how we bill our patient encounters ever since.

Unfortunately, efforts to advance diversity, equity, and inclusion have faced pushback.[8] Although data show that diversity improves health outcomes and even makes corporations more profitable,[9,10] some still come to the discussion with a staunch, "Why do we need to focus on this?" *Harvard Business Review* published an excellent article answering that very question and offering pointed rebuttals to explain the resistance.[8]

Diversity, equity, and inclusion is not a zero-sum game. As retina physicians, we are skilled in managing the most complex cases. The more we look for ways to include and retain talented individuals from all backgrounds, nourish this talent, and amplify diverse voices in leadership to help us tackle the complex realm of vitreoretinal disease, the stronger we will be. And our patients deserve nothing less. ■

– Adrienne W. Scott, MD, and Steve Sanislo, MD

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FURTHER READING

LGBTQ+ Pearls for Colleagues

A discussion with Jessica Weinstein, MD; Roberto Diaz-Rohena, MD; Steve Sanislo, MD; and Brandon Johnson, MD; Moderated by Vivienne S. Hau, MD, PhD; and Basil K. Williams Jr, MD

Accepting Transitions in Retina

By Vivienne S. Hau, MD, PhD

TABLE OF CONTENTS

Diversity *and* Inclusion

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WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA[1]

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data[1]

Over 60% of wet AMD "fellow eyes" lose too much vision[1]– even with frequent treatment visits

Detect Early. Treat Early.

ForeseeHome is a **remote monitoring** program for at-risk wet AMD fellow eyes that helps **detect conversion** at 20/40 or better in 83% of patients.[2]

- FDA Cleared
- Medicare Covered

ForeseeHOME™
AMD Monitoring Program

Introduce your patients to ForeseeHome during an injection visit and offer them an extra level of protection.

Our Monitoring Center works with your staff to easily implement an "inject and protect" protocol into your practice workflow that requires minimal effort or additional time.

The Key to Successful Home Monitoring

NOTAL VISION MONITORING CENTER

- Engagement & Education
- Benefits Verification & Authorization
- Continuous Monitoring

NOTAL VISION™
Monitoring Center

- Practice Workflow Implementation
- Remote Patient Management
- Vision Alert Management

References: 1. Ho AC, Kleinman DM, Lum FC, et al. Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51:633-639. **2.** Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, American Society of Retina Specialist Meeting 2020.

See website for FDA Indication for Use.

SM-125.3

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RT NEWS

MARCH 2024

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AMD LINKED WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES

While faulty complement activation is implicated in AMD and many systemic immune-mediated inflammatory diseases, the relationship between AMD and these various conditions remains unclear. Looking to close this gap, a recent study published in *Ophthalmology Retina* found an increased risk of developing AMD in patients with certain immune-mediated inflammatory diseases.[1]

The cross-sectional study evaluated an AMD cohort and a control group (n = 217,197 each) and included propensity score matching based on age, sex, race, ethnicity, and smoking status. The main outcome measures included the odds ratio of immune-mediated inflammatory disease, risk ratios (RR), and confidence intervals of AMD diagnosis given an immune-mediated inflammatory disease.[1]

The team found that AMD was associated with systemic lupus erythematosus, Crohn disease, ulcerative colitis, rheumatoid arthritis, psoriasis, sarcoidosis, scleroderma, giant cell arteritis, and vasculitis. After creating cohorts for each of these associated diseases, the researchers matched them to control cohorts without a history of immune-mediated inflammatory disease, and found that patients with rheumatoid arthritis (RR: 1.40), systemic lupus erythematosus (RR: 1.73), Crohn disease (RR: 1.42), ulcerative colitis (RR: 1.45), psoriasis (RR: 1.48), vasculitis (RR: 1.48), scleroderma (RR: 1.65), and sarcoidosis (RR: 1.42) were all at a higher risk of developing AMD compared with controls.[1]

Be mindful of a potential relationship with AMD when assessing patients with immune-mediated inflammatory diseases who may develop ocular comorbidities, the researchers concluded in their paper.[1]

1. Shukla P, Russell MW, Muste JC, et al. Propensity matched analysis of the risk of age-related macular degeneration with systemic immune-mediated inflammatory disease [published online ahead of print February 3, 2024]. *Ophthalmol Retina*.

MACHINE LEARNING IDENTIFIES DR PROGRESSION USING UWF IMAGING

A recent study published in *JAMA Ophthalmology* reported on the accuracy and feasibility of automated machine-learning models in identifying diabetic retinopathy (DR) progression with ultra-widefield (UWF) images, especially for the prediction of 2-step or greater DR progression within 1 year.[1]

A total of 1,179 UWF images with mild (380 [32.2%]) or moderate (799 [67.8%]) nonproliferative DR (NPDR) were included. DR progression was present in half of the training set (590 of 1,179 [50.0%]). The model's area under the precision-recall curve was 0.717 for baseline mild NPDR and 0.863 for baseline moderate NPDR. In regard to the validation set for eyes with mild NPDR, sensitivity was 0.72 (95% confidence interval [CI]: 0.57-0.83), specificity was 0.63 (95% CI: 0.57-0.69), prevalence was 0.15 (95% CI: 0.12-0.20), and accuracy was 64.3%. For eyes with moderate NPDR, sensitivity was 0.80 (95% CI: 0.70-0.87), specificity was 0.72 (95% CI: 0.66-0.76), prevalence was 0.22 (95% CI: 0.19-0.27), and accuracy was 73.8%. In the validation set, six of nine eyes (75%) with mild NPDR and 35 of 41 eyes (85%) with moderate NPDR that progressed by at least 2 steps were identified by the machine-learning algorithm. All four eyes with mild NPDR that progressed within 6 months and 1 year were identified, and eight of nine eyes (89%) and 17 of 20 eyes (85%) with moderate NPDR that progressed within 6 months and 1 year, respectively, were identified.[1]

The use of machine-learning algorithms may refine the risk of disease progression and help identify patients at the highest short-term risk, reducing costs and improving vision-related outcomes, the abstract noted.[1]

1. Silva PS, Zhang D, Jacoba CMP, et al. Automated machine learning for predicting diabetic retinopathy progression from ultra-widefield retinal images [published online ahead of print February 8, 2024]. *JAMA Ophthalmol*.

GA LESION LOCATION ASSOCIATED WITH QUALITY OF LIFE

An international team of researchers recently published results of their study highlighting the significance of the location of geographic atrophy (GA) lesions in determining patients' vision-related quality of life. The importance of

low-luminance visual acuity was even more pronounced in patients with fovea-sparing GA, they found.[1]

The prospective, non-interventional, natural-history study included 82 patients with bilateral GA. Relevant parameters were correlated with vision-related quality of life, which was gauged using the National Eye Institute Visual Function Questionnaire 25.[1]

On average, patients showed a total GA area of 2.9 ± 1.2 mm^2 in the better eye and 3.1 ± 1.3 mm^2 in the worse eye. The most significant associations with vision-related quality of life scores for distance and near activities were observed in the inner lower and inner left subfields of the better eye, respectively. For patients with fovea-sparing GA, the low-luminance visual acuity of the better eye was the most influential variable across all vision-related quality of life scales.[1]

The researchers concluded that a better understanding of the association between lesion location and patient-reported outcomes is necessary to inform treatment decisions and dictate interventional trial parameters.

1. Künzel SH, Broadbent E, Möller PT, et al. Association of lesion location and functional parameters on vision-related quality of life in geographic atrophy secondary to AMD [published online ahead of print February 2, 2024]. *Ophthalmol Retina.*

AI MATCHES OR OUTPERFORMS RETINA, GLAUCOMA SPECIALISTS

Researchers at Mount Sinai recently studied the diagnostic accuracy and comprehensive responses of a large-language model (LLM) chatbot (GPT-4, version dated May 12, 2023), and found that it outperformed glaucoma specialists and matched retina specialists when it came to diagnostic and treatment accuracy.[1]

The study included 12 attending physicians and three senior trainees; 10 glaucoma and 10 retina questions randomly selected from the AAO's Commonly Asked Questions; and deidentified glaucoma and retinal cases (10 each). To assess the accuracy of the LLM on the ophthalmic questions and patient case management, the researchers prompted the model to provide answers as a "medical assistant, delivering concise answers to emulate an ophthalmologist's response." One investigator prompted the LLM with the questions and cases, asking the tool to provide a clear assessment and plan that reflected the medical record documentation format.[1]

Using a 10-point Likert scale to assess accuracy, the researchers found that the combined question-case mean rank for accuracy was 506.2 and 403.4 for the LLM chatbot and glaucoma specialists, respectively ($P < .001$). The mean rank for completeness was 528.3 and 398.7, respectively ($P < .001$). As for retina specialists, the mean rank for accuracy was 216.1 compared with 235.3 for the LLM chatbot ($P = .17$), and the mean rank for completeness was 208.7 compared with 258.3 for the chatbot ($P = .005$). The findings revealed differences between specialists and trainees in both accuracy and completeness scoring. Using Dunn's pairwise comparisons, the study found that trainees and specialists rated the chatbot's accuracy and completeness more favorably than those of the specialists.[1]

Based on this data, the team concluded that the LLM chatbot performed favorably, matching retina specialists in accuracy but exceeding them in completeness. The model showed superiority in glaucoma diagnosis and treatment compared with fellowship-trained specialists.[1]

"The enhanced performance of the chatbot in our study compared with other evaluations could be attributed to the refined prompting techniques used, specifically instructing the model to respond as a clinician in an ophthalmology note format," the researchers concluded in their paper.[1]

1. Huang AS, Hirabayashi K, Barna L, Parikh D, Pasquale LR. Assessment of a large language model's responses to questions and cases about glaucoma and retina management [published online ahead of print February 22, 2024]. *JAMA Ophthalmol.*

SHORT-ACTING TAMPONADES PROVE EFFECTIVE FOR RRD REPAIR

Researchers recently assessed the outcomes of vitrectomy using either long- or short-acting gas tamponades and found comparable success rates of retinal reattachment for each group. Traditionally, long-acting gas tamponades, such as C_3F_8 or C_2F_6, have been thought to improve surgical success rates of rhegmatogenous retinal detachment (RRD) repair due to their prolonged effect compared with short-acting gas tamponades, such as SF_6.[1]

The team retrospectively analyzed 533 eyes of 524 patients from two study sites who were diagnosed with primary RRD not complicated by proliferative vitreoretinopathy. Retinal redetachment rates 6 months following surgery were analyzed.[1]

At study site one, 254 of 278 eyes (91.4%) were treated with a long-acting gas tamponade (C_3F_8, 72.3%; C_2F_6, 19.1%); at study site two, 246 of 255 eyes (96.5%) received SF_6. Rates of retinal redetachment in the long- and short-acting tamponade groups were similar: 23 of 254 eyes (9.1%) and 24 of 246 eyes (9.8%), respectively. Median time to redetachment was 5.7 weeks in the long-acting tamponade group and 4.4 weeks in the short-acting tamponade group.[1]

The authors concluded that a short-acting gas tamponade is a reasonable choice when treating RRD without proliferative vitreoretinopathy.[1]

1. Schöneberger V, Li JQ, Menghesha L, Holz FG, Schaub F, Krohne TU. Outcomes of short- versus long-acting gas tamponades in vitrectomy for rhegmatogenous retinal detachment [published online ahead of print February 5, 2024]. *Int J Retina Vitreous.*

OCTA BIOMARKERS PREDICT RISK OF EXUDATIVE CONVERSION IN GA

After investigating the incidence and morphological biomarkers of exudative conversion in eyes with type 1 nonexudative macular neovascularization using OCT angiography (OCTA), researchers found that, at 12 months, the risk of conversion was 22.5%. An "anastomosis and loops" pattern and increased vessel density were useful OCTA biomarkers for predicting conversion, they noted.[1]

Depending on whether exudation developed within 1 year, the eyes were divided into two groups: active and silent. Qualitative and quantitative OCTA parameters of the two groups were evaluated to determine the biomarkers associated with conversion.[1]

Of the 40 eyes in the study, nine developed exudation within 1 year (incidence rate of 22.5%). The active group exhibited a more significant "anastomosis and loops" pattern, greater vessel and junction density, fewer number of endpoints, and lower lacunarity compared with the silent group. The pattern and higher vessel density were correlated with the active group in multivariate analyses. A predictive model combining these biomarkers achieved 95% accuracy in predicting exudative conversion.[1]

"For eyes with a high risk of exudative conversion, more frequent follow-up is recommended," the team stated in their paper.[1]

1. Bae SH, Bae K, Yoon CK, Park UC, Park KH, Lee EK. Morphological biomarkers predicting exudative conversion in type 1 nonexudative macular neovascularization using OCT angiography [published online ahead of print February 12, 2024]. *Retina*.

DATA SHOWS SUSTAINED VISUAL GAINS IN RETINAL VEIN OCCLUSION THERAPY

Genentech/Roche recently announced results from two global phase 3 studies, BALATON and COMINO, evaluating faricimab-svoa (Vabysmo, Genentech/Roche) in the treatment of macular edema due to branch and central retinal vein occlusion. Findings showed that almost 60% of patients treated with faricimab-svoa in BALATON and 50% in COMINO were able to extend their treatment intervals to 3 or 4 months. The vision gains and robust retinal drying achieved in the first 24 weeks of the studies were maintained for up to 72 weeks.[1]

At 72 weeks in the BALATON study, patients receiving faricimab-svoa as a first-line treatment gained 18.1 letters, while patients who switched from aflibercept (Eylea, Regeneron) to faricimab-svoa gained 18.8 letters. Patients treated initially with faricimab-svoa also saw a 310.9 µm reduction in central subfield thickness (CST), while those who switched from aflibercept to faricimab-svoa saw a reduction in CST of 307 µm.[1]

In the COMINO study, patients receiving faricimab-svoa gained 16.9 letters at 72 weeks, while patients who switched from aflibercept to faricimab-svoa gained 17.1 letters. These patients also saw a 465.9 µm reduction in CST, while those who switched from aflibercept to faricimab-svoa saw a reduction of 460.6 µm.[1] ■

1. New long-term data for Genentech's Vabysmo show sustained retinal drying and vision improvements in retinal vein occlusion (RVO). Genentech. January 31, 2024. Accessed February 15, 2024. www.gene.com/media/press-releases/15017/2024-01-31/new-long-term-data-for-genentechs-vabysm

Eyewire+ Pharma Update

- **Théa Open Innovation** obtained development and commercialization rights to **KIO-301** for the treatment of retinal degenerative diseases from Kiora Pharmaceuticals.
- The first patient has been dosed in part 2 of the phase 2/3 SIGLEC trial of **AVD-104 (Aviceda Therapeutics)** for the treatment of geographic atrophy (GA). The trial will evaluate the safety and efficacy of AVD-104 versus an active comparator, avacincaptad pegol (Izervay, Iveric Bio/Astellas), with a primary endpoint of change in the growth rate of GA area over 12 months.
- **Adverum Biotechnologies** recently announced positive preliminary safety and efficacy data from the phase 2 LUNA trial of **ixoberogene soroparvovec (Ixo-vec)** intravitreal gene therapy for the treatment of wet AMD. Each dose cohort in the trial significantly reduced treatment burden while maintaining visual acuity and anatomic endpoints.
- **4D Molecular Therapeutics** announced positive interim data from the phase 2 PRISM trial evaluating intravitreal **4D-150** in patients with wet AMD. Patients dosed with 4D-150 experienced significant reduction in treatment burden of anti-VEGF injection.
- Positive 12-month interim safety and efficacy data from the phase 2 SKYLINE trial of **AGTC-501 (Beacon Therapeutics)** for the treatment of X-linked retinitis pigmentosa showed that 63% of patients treated with the high dose experienced an improvement in retinal sensitivity of at least 7 decibels in at least five loci.
- **Opthea** recently completed enrollment of all patients in its COAST phase 3 pivotal clinical trial investigating **sozinibercept (OPT-302)**, a VEGF-C/D inhibitor in combination with aflibercept (Eylea, Regeneron), for the treatment of wet AMD. Enrollment in ShORe is expected to be completed in Q2 2024.
- The first three patients received their first injection in the phase 3 SOL-1 clinical trial of **axitinib intravitreal implant/OTX-TKI (Axpaxli, Ocular Therapeutix)** for the treatment of wet AMD. The novel therapy is a bioresorbable, hydrogel implant incorporating axitinib, a tyrosine kinase inhibitor with anti-angiogenic properties.

MATTHEW R. STARR, MD

WHERE IT ALL BEGAN

I was born and raised in Oklahoma City, Oklahoma, but attended college at St. Louis University in Missouri, where I was accepted into a program that guaranteed my acceptance into medical school out of high school. I grew up knowing that I wanted to become a physician because my dad was a general practioner in Oklahoma before passing away.

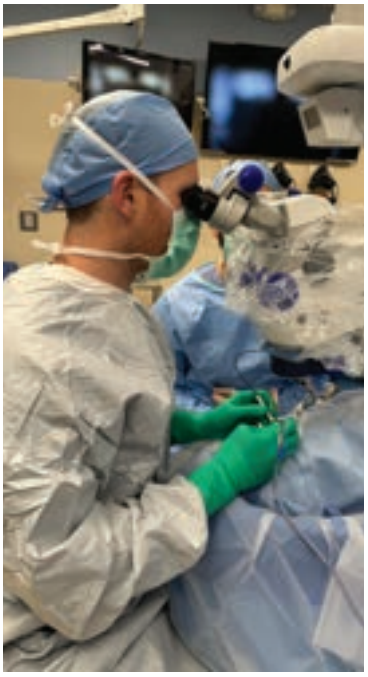
MY PATH TO RETINA

I went into medical school thinking I wanted to become an interventionist or surgeon. However, during my first year of medical school, a lecture by Sophia Chung, MD, a neuro-ophthalmologist (now at the University of Iowa), opened my eyes to the field of ophthalmology and changed my trajectory. Then, during my third year of medical school, I shadowed a retina surgeon, and I was hooked. I enjoyed other rotations during residency, but from the start I always knew I wanted to do retina. I like being able to do everything in the eye and being the last line of defense when things go south.

SUPPORT ALONG THE WAY

So many people have been instrumental in my career. My current chair, Sophie J. Bakri, MD, MBA, was my mentor during residency and molded me into who I am today from an academic standpoint. Dr. Bakri demands perfection, and she held me accountable during residency to strive to be the best. In fellowship at Wills Eye Hospital in Philadelphia, I was fortunate to learn from Allen C. Ho, MD; Carl D. Regillo, MD; Arunan Sivalingam, MD; Richard S. Kaiser, MD; Marc J. Spirn, MD; James P. Dunn, MD; Jason Hsu, MD; James Vander, MD; Carl H. Park, MD; Sonia Mehta, MD; Allen Chiang, MD; Mitchell Fineman, MD; Omesh P. Gupta, MD; Michael A. Klufas, MD; Yoshihiro Yonekawa, MD; Ajay E. Kuriyan, MD, MS; and Michael N. Cohen, MD. I still connect with these mentors regularly to discuss various problems and patient encounters. Now in practice, I try to emulate Dr. Yonekawa's clinical and research habits—something no one can really do. He has always pushed me to critically evaluate my research and how I can move the field forward.

Dr. Starr's advice: To quote Charles P. Wilkinson, MD, "Read all you can, do all you can, assist all you can." Retina is hard; you must stay late, see that extra patient, and do the extra project because that is how you learn and develop relationships that will continue to guide you along your career path.



AN EXPERIENCE TO REMEMBER

The hardest part after fellowship was learning to deal with complications. Ten months after fellowship, I did a perfect surgery in a young teenager who developed a terrible complication 2 weeks postoperatively and another set of issues almost 1 year later that no one could have predicted. This patient has lost a considerable amount of vision in both eyes. When discussing the most recent issues with the family, I asked if they wanted me to leave so that they could discuss their options, and they replied, "You are part of the family now." Despite everything this family had been through, they still put their child's eyes in my hands to fix. This experience is one of the many reasons why I do what I do. ■

Matthew R. Starr, MD, is an assistant professor of ophthalmology at the Mayo Clinic in Rochester, Minnesota, and will be the associate director for the residency program starting July 2024. He primarily practices adult surgical retina and has a strong interest in secondary IOL techniques and quality improvement and patient safety. Dr. Starr is a consultant for Gyroscope Therapeutics and is on the advisory boards for Abbvie, Alimera Sciences, Genentech/Roche, and Regenxbio. He can be reached at **mstarr1724@gmail.com**.

A SURGICAL APPROACH TO VASOPROLIFERATIVE TUMORS

This case example shows why taking some patients to the OR may be the best option.

BY SAMANTHA GOLDBURG, MD; JENNIFER ADEGHATE, MD; AND TALIA R. KADEN, MD

Retinal vasoproliferative tumors (RVPT) are benign, vascularized peripheral retinal lesions that may occur incidentally or in association with inflammatory or ischemic processes.[1-3] Smaller, asymptomatic RVPT can be observed,[2] but larger lesions, particularly those causing exudative or tractional retinal detachment (TRD), macular edema, vitreous hemorrhage, or epiretinal membranes (ERM), may require treatment for the best results.[3-5]

Management options include cryotherapy, laser photocoagulation, brachytherapy, or pars plana vitrectomy (PPV) and surgical resection of the tumor for those with vision-threatening sequelae.[6] While most of the literature supports starting with conservative management, there is a growing body of data showing that surgical intervention is safe and effective for these patients.

Here, we review the surgical approaches to RVPT associated with TRD and ERM, discuss current techniques, and provide insights from a recent case.[7]

THE CASE

A 71-year-old woman with RVPT presented with a VA of counting fingers and an extensive ERM that resulted in a TRD of most of the inferior posterior pole (Figure 1).[7] We elected to perform cataract surgery in combination with PPV to enhance visualization of the retina, avoid maneuvering around the phakic eye, and improve access to the peripheral retina and vitreous base.[8]

Microcannula placement is an important consideration, and we opted to place the infusion microcannula inferonasally to avoid the inferotemporal lesion and improve access to it intraoperatively.[7] We began with anterior-posterior segmentation of the vitreous. After we isolated the posterior pole, we initiated the ERM peel. We prefer to use (and recommend) a bent 25-gauge needle, as it allows for the creation of an entry point in the overlying membrane without disturbing the underlying retinal tissue.

We removed the ERM, which extended further into the midperiphery than we had initially anticipated. Due to the integration of the ERM into the retina around the optic nerve, we trimmed the membrane rather than remove it completely, as this would not have facilitated our efforts to eliminate retinal traction and most likely would have led to unnecessary retinal tissue loss (Figure 2).

Several papers report limited benefit of aggressive membrane peeling not only from a macroscopic perspective (eg, retinal tears or detachment),[9] but also on a microscopic level. For instance, Ehlers et al noted both focal inner retinal swelling and inner retinal thinning in the acute postoperative period following the internal limiting membrane (ILM) peel associated with instrument-tissue interaction;[10] however, the functional implications of these architectural changes remain unclear. We stained the ILM with ICG and peeled it up to the arcades to reduce the risk of postoperative ERM recurrence.[11]

On scleral depression, we also noted a localized retinoschisis cavity surrounding the RVPT without outer retinal breaks. We decided not to drain the cavity, regarding this as uncomplicated retinoschisis with a low risk for progression.[12] We performed a fluid-air exchange to help with wound closure and to provide a tamponade for subretinal fluid displacement.[13,14] We advised the patient to position herself temporal side down for an hour and face down for 3 days.

Lastly, we used endophotocoagulation to ablate the tumor.[6] Postoperatively, the patient's VA improved to 20/100 at 3 months, refracted to 20/60, and the retina remained flat and without ERM recurrence.

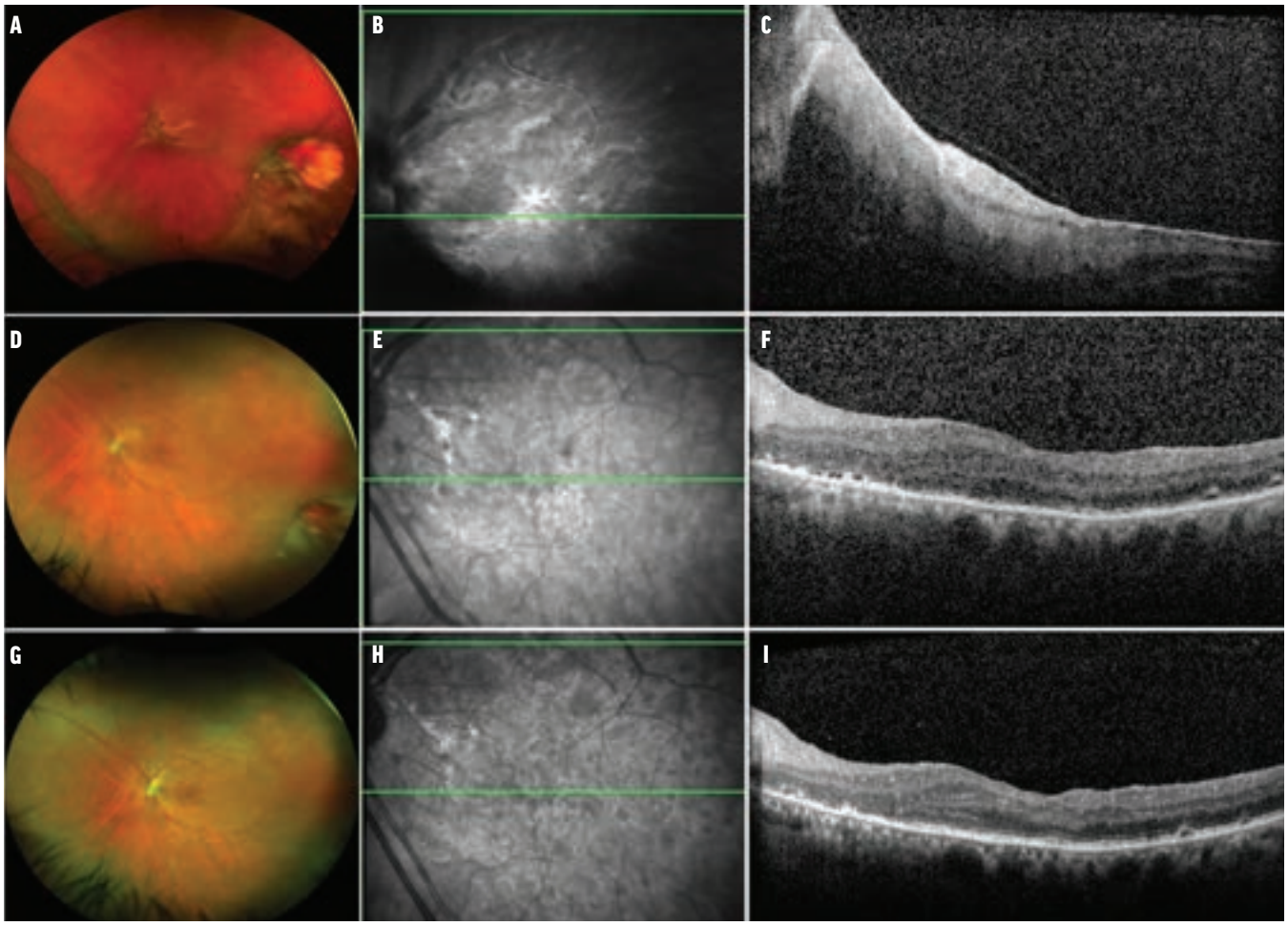


Figure 1. Preoperative fundus photography and spectral-domain OCT imaging show an inferotemporal RVPT (A) with ERM and TRD (B, C). One month postoperatively, there is regression of the RVPT (D) and flattening of the retina on OCT (E, F). At 3 months postoperatively, the fundus photograph (G) captures the edge of the regressed RVPT, and the retina remains flat (H, I).

DISCUSSION

Although asymptomatic RVPT can be observed, any visually significant sequelae must be addressed promptly, particularly macula-involving TRD. Our patient presented after several years lost to follow-up, during which her TRD had markedly progressed. At the time of surgery, our primary goal was macular reattachment by reducing traction, which was achievable without tumor resection.

There are several approaches to tractional elements in these cases, which may differ between patients. Case reports of RVPT and associated ERM, retinal detachment, or vitreous hemorrhage have described successful PPV with scleral buckles;[2] however, we decided against buckling because there were no outer retinal breaks seen on scleral depression, and the main cause of the TRD was deemed to be overlying traction from the ERM, which we planned to remove.

There have also been reports of RVPT occurring in a patient with X-linked uveitic retinoschisis,[15] which our patient did not have. We believe that the unusual adherence of the tissue planes and the resulting ERM may have contributed to the schisis cavity itself, which, along with the absence of outer retinal breaks, deterred us from approaching the schisis as a surgical problem. Additionally, while spontaneous release of ERM associated with RVPT has been reported after laser photocoagulation and cryotherapy,[16] we did not think this would occur in our case, given the adherence and density of the ERM.

One case series had worse visual outcomes after RVPT excision,[2] while another series report better long-term visual acuity in those who underwent tumor resection during PPV.[17] Ultimately, whether these lesions warrant resection should be left to the surgeon's judgement of how contributory they are to the overall pathology and the potential risks to the patient.[18]

SURGICAL SUCCESS

Our case contributes to the growing body of literature reporting favorable outcomes following PPV for the treatment of symptomatic RVPT. As has been reported elsewhere,[2] our case also suggests that patients who are

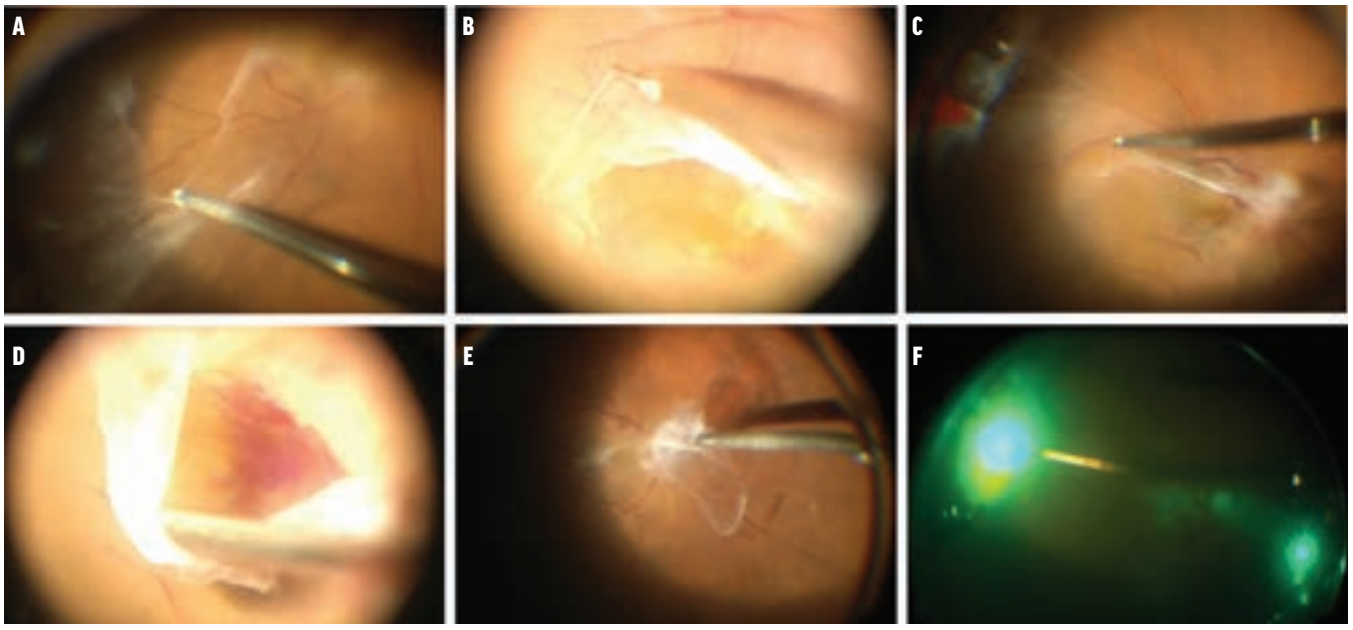


Figure 2. Intraoperatively, the surgeon performed anterior-posterior segmentation of the stiffened hyaloid and peeled the thick ERM (A-C). After the ERM was peeled, the surgeon segmented (D) and trimmed the membrane at the optic nerve (E). The lesion itself was treated with endophotocoagulation alone (F).

THERE IS A GROWING BODY OF DATA SHOWING THAT SURGICAL INTERVENTION IS SAFE AND EFFECTIVE FOR THESE PATIENTS.

managed conservatively may eventually require surgery due to vision-threatening sequelae. Vitrectomy in patients with RVPT can be safe and effective, but may require creative surgical approaches to address the many components of this complex entity.[5,7] ■

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RETINAL CAPILLARY HEMANGIOBLASTOMAS IN VHL

Case studies suggest a novel therapeutic may be able to treat these vision-threatening ocular tumors.

BY CORRINA P. AZARCON, MD, DPBO; IMAAN ZERA KHERANI, MD; AND AMIN KHERANI, MD, FRCSC, FASRS

Von Hippel-Lindau (VHL) is an autosomal dominant neurocutaneous syndrome characterized by the growth of vascular tumors throughout the body, including the kidneys, pancreas, brain, spine, and eyes. This rare genetic mutation is found in one out of 36,000 individuals, and at least 900 cases have been reported in Canada.[1,2] A key mechanism of VHL involves angiogenesis in normoxic conditions due to inactivation of the VHL protein via germline mutations of the VHL tumor suppressor gene. The inactivated VHL protein loses its ability to degrade hypoxia-inducible factors (HIF), leading to the formation of stable HIF subunits, activation of HIF-mediated transcription, and VEGF production.[2-5]

OCULAR TUMORS ASSOCIATED WITH VHL

Ocular manifestations affect approximately half of patients with VHL and are diagnosed at a mean age of 26 years.[6,7] Retinal capillary hemangioblastomas (RCHs) are the most common, with an 80% chance after age 80.[2,7,8] RCHs typically present unilaterally or bilaterally in the peripheral retina or juxtapapillary area. These lesions can lead to vision-threatening complications, such as retinal nonperfusion and exudative or tractional retinal detachments (RDs).[7,9]

Treatment of RCHs is indicated when the vision is compromised; otherwise, small peripheral tumors are monitored.[10,11] Ablative treatment modalities, such as laser, cryotherapy, transpupillary thermotherapy, photodynamic therapy, plaque brachytherapy, and external beam radiotherapy, are employed in cases of tumor progression.[2] Surgical resection may be warranted for larger tumors, and intravitreal anti-VEGF therapy may be used as an adjunctive treatment to control exudation and retinal edema.[2,11] While smaller and peripheral tumors respond well to local treatment, large or juxtapapillary tumors may be refractory.[11]

Belzutifan (Welireg, Merck), a small-molecule HIF-2α inhibitor that effectively blocks HIF pathway activation, inhibits VEGF-driven angiogenesis and tumor progression. This novel drug is already approved for nonsurgical renal cell carcinoma, central nervous system (CNS) hemangioblastomas, and pancreatic neuroendocrine tumors in patients with VHL.[12,13] While RCHs have not been specifically identified as an indication for the initiation of belzutifan, reports are beginning to shed light on its potential benefits for patients with RCH who are also dealing with other VHL-associated tumors.[14-16]

In this report, we present a patient with VHL and bilateral RCHs alongside systemic tumors, whose ocular tumors responded favorably to treatment with oral belzutifan.

CASE REPORT

A 30-year-old woman with genetically confirmed VHL syndrome has been followed for 2 decades in our retina clinic due to RCHs. She established care with our institution at 11 years of age, at which time she was asymptomatic and had a VA of 20/20 OU. She was diagnosed with a peripapillary RCH in her left eye, which was initially observed.

Over the next 4 years, her vision gradually worsened to a VA of 20/100 OS secondary to tumor growth, bleeding, and exudation. Intravitreal anti-VEGF injections resulted in temporary improvement of the retinal edema. However, due to subsequent progressive tumor growth, her left eye eventually underwent plaque brachytherapy. Photodynamic therapy was also performed 1 year later. She then developed a tractional and exudative RD in her left eye, which required vitrectomy, subretinal fluid drainage, and oil tamponade. Despite these efforts, the retina redetached, and her left eye developed neovascular glaucoma, resulting in complete left visual field loss 11 years after her initial presentation.

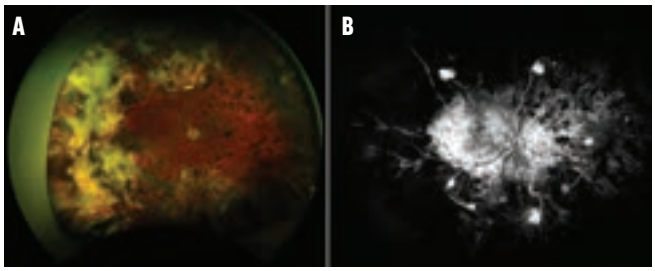

Figure 1. A wide-angle fundus photo of the right eye 17 years after initial presentation showed extensive peripheral retinal scarring after multiple retinal reattachment procedures and ablative treatment of RCHs (A). An arterial-phase FA of the right eye revealed the presence of multiple, perfused RCHs in the retinal periphery within the scarred areas of the retina (B).

Development of Bilateral Disease

The first RCH in the patient's right eye was documented approximately 6 years after her initial evaluation. During this time, she presented with flashes and floaters, although her VA was 20/20 OD. A solitary tumor in the superotemporal retinal periphery was treated with focal laser ablation. After four treatment sessions, she developed a tractional and exudative RD, which warranted vitrectomy, peeling, laser, cryotherapy, and gas tamponade. The retina was successfully reattached, and she attained a postoperative VA of 20/25 OD.

The right eye remained stable for the next 5 years, at which point she developed a new RCH and associated tractional RD. She was treated with a combined buckle-vitrectomy procedure, membrane peeling, retinectomy, endolaser, and gas tamponade. Another retinal reattachment surgery was performed 8 months later, ultimately achieving anatomic reattachment and a VA of 20/60 OD.

Long-Term Follow-Up

Fifteen years after her initial presentation, the patient continued to develop multiple RCHs in the retinal periphery of her right eye. She underwent repeat laser ablation procedures, even in previously treated areas. Wide-angle fundus photography at follow-up year 17 showed peripheral chorioretinal scarring and fibrosis, along with a focal tractional band and detachment inferiorly in the right eye (Figure 1A). Fluorescein angiography (FA) confirmed the presence of multiple perfused RCHs in the retinal periphery (Figure 1B), most of which were not visible on fundus examination. These were periodically treated with focal laser.

At year 19 of follow-up, continued growth of the patient's RCHs resulted in vitreous hemorrhage in the right eye, which caused her VA to decrease to 20/80 OD.

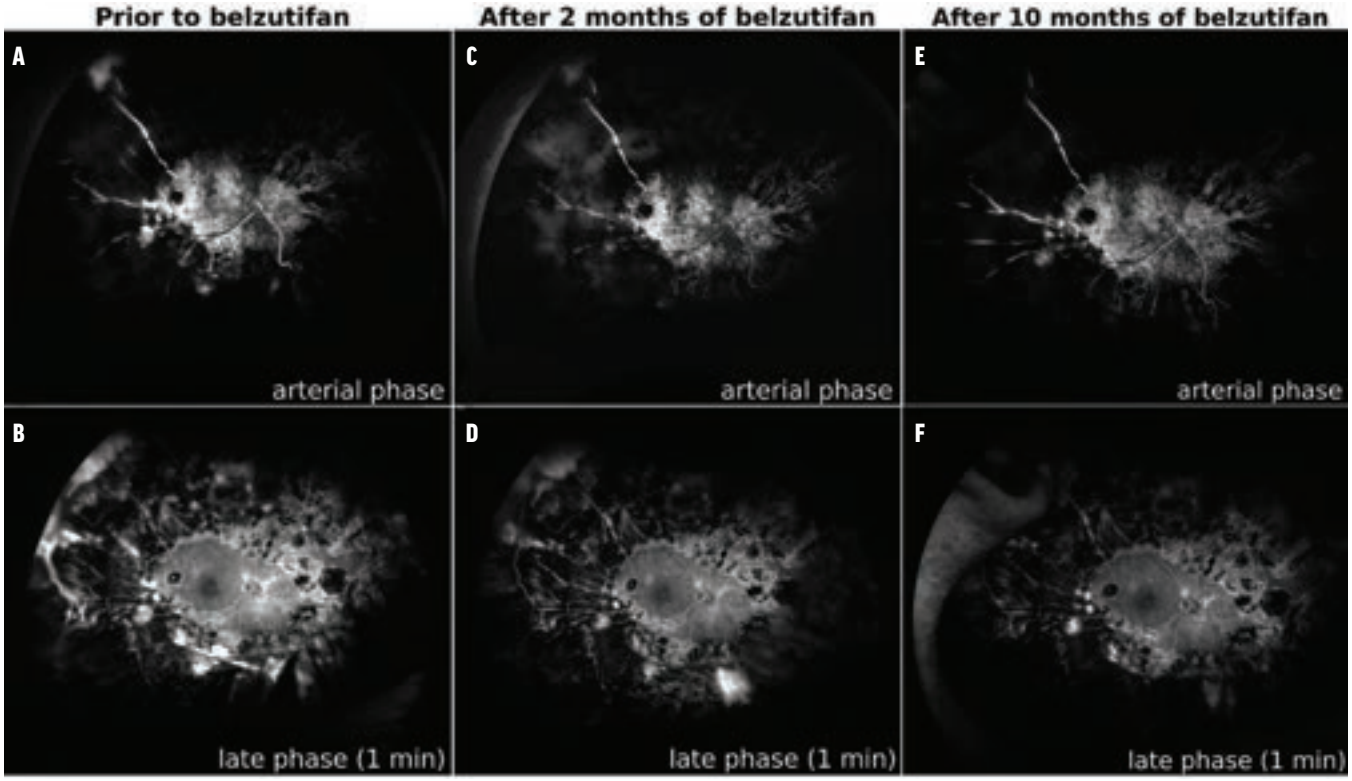

Figure 2. An arterial-phase FA prior to belzutifan initiation demonstrated hyperfluorescence of the RCHs and prominent feeder vessels (A, B). A repeat scan after 2 months of oral belzutifan showed decreased tumor hyperfluorescence and narrowing of the feeder vessels supplying the RCHs, particularly in the temporal and inferior periphery (C, D). Another scan 10 months after belzutifan initiation showed no new tumors (E, F). Note the heightened visibility of the temporal vessel in C compared with B, which can be attributed to alterations in image contrast settings. Upon thorough review of all photos, there were no newly identified tumors in the temporal periphery.

A New Treatment Approach

Throughout her disease course, this patient was managed for several VHL-associated tumors: bilateral adrenal pheochromocytomas, pancreatic neuro-endocrine tumors, CNS hemangioblastomas, intracranial meningioma, spinal intramedullary hemangioblastomas, and renal cell carcinoma. A recent abdominal MRI indicated enlargement of her right renal cell carcinoma, coinciding with the right-eye vitreous hemorrhage (Figure 2A and B).

Following discussions with her medical oncologist, 120 mg oral belzutifan was initiated once daily. After 2 months of this treatment regimen, her RCHs demonstrated a favorable response (Figure 2C and D). However, she also developed symptomatic anemia, and her hemoglobin decreased to 87 mg/dL. Belzutifan was temporarily discontinued for 1 week, and she underwent infusion of two units of packed red blood cells. At present, she remains systemically stable on a reduced dose of 80 mg oral belzutifan once daily. At her latest ophthalmic examination, her VA was 20/50 OD. A follow-up FA performed 10 months after initiating belzutifan showed no new RCHs (Figure 2E and F).

DISCUSSION

Our report contributes to the growing body of evidence demonstrating the regression of RCHs following treatment with oral HIF-2α inhibitors,[14-15] which has typically been initiated to address other types of VHL-associated tumors. Such reports suggest the effectiveness of oral HIF-2α inhibitors as an option for managing refractory RCHs, as was demonstrated with our patient.

Barriers to Treating RCHs With Oral Belzutifan

While CNS hemangioblastomas are listed in the current guidelines for initiation of belzutifan, RCHs are not recognized as an independent indication for oral belzutifan therapy. One anticipated barrier is the substantial cost associated with oral belzutifan treatment, especially given the prevalence of RCHs among patients with VHL. However, for patients with only one seeing eye or who develop bilateral vision-threatening RCHs, oral belzutifan may be the only hope to prevent total blindness.

While most patients who initiate treatment for alternative indications begin with a daily dose of 120 mg, some patients may need a lower dose due to adverse effects. Large-scale, comprehensive studies are warranted to investigate the minimum effective dose to treat or stabilize RCHs.

Imaging Pearls

While fundoscopy and wide-angle fundus imaging remains valuable, it was inadequate in monitoring areas of the retina that had become obscured by scarring. Periodic FA is crucial in documenting changes in tumor size and vascularity,[16] especially in areas difficult to assess clinically.

HOPE AMID A LIFETIME RISK FOR TUMORS

VHL syndrome predisposes individuals to developing tumors across multiple organ systems over their lifetime. Currently, RCHs are not listed as an independent indication for initiating belzutifan therapy. Our case is a compelling example of a positive response of RCHs to oral belzutifan. Future research will provide valuable insights into the potential of oral HIF-2α inhibitors as a game-changing therapeutic option for patients with vision-threatening VHL-associated RCHs. ■

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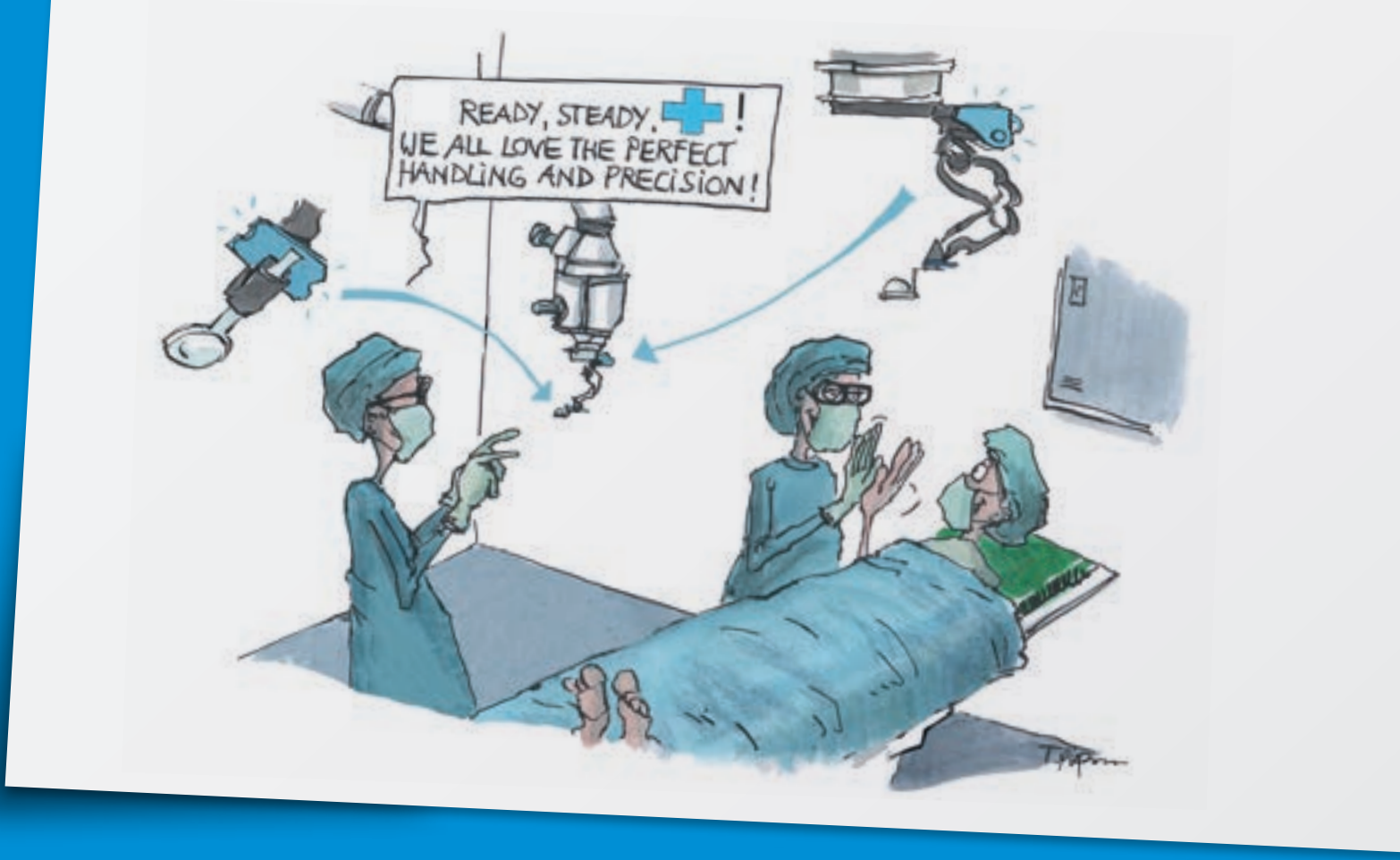

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Diversity in Retina Leadership

Where are the Women Now?



An interview with Julia A. Haller, MD.
By Adrienne W. Scott, MD, and Steve Sanislo, MD

Julia A. Haller, MD, and her team have been tireless in their pursuit of diversity, equity, and inclusion (DEI) in retina, particularly within research, authorship, and editorial positions. Here, Adrienne W. Scott, MD, and Steve Sanislo, MD, discuss with Dr. Haller the state of affairs in retina and just how far we have come—and how much is left to do.

- Rebecca Hepp, Editor-in-Chief

Adrienne W. Scott, MD: Your 2015 editorial in *JAMA Ophthalmology*, Cherchez la Femme, was the first of its kind in a high-impact, peer-reviewed journal.[1] When I read it, I was heartened, as a woman starting out in the field of vitreoretinal surgery, because I thought that if you were identifying a problem, bringing it to the attention of our field, and offering solutions, it's a very important issue.

DR. SCOTT: AS WE LOOK BACK ALMOST 10 YEARS, WHAT IS YOUR PERSPECTIVE ON WHERE WE ARE NOW?

Julia A. Haller, MD: I think we've made progress. An important piece has been recognizing that there's an issue and then getting metrics so that we can think of ways to

AT A GLANCE

- The 2015 editorial in *JAMA Ophthalmology*, Cherchez la Femme, written by Julia A. Haller, MD, was the first of its kind in a high-impact, peer-reviewed journal.
- Dr. Haller's research shows that, between 2015 and 2019, there was a definite increase in the number of women editorialists.
- One study found that women were significantly underrepresented in terms of engagement with industry, and when women were involved, they were paid less.
- Research on corporate board diversity found that, boards with more women were more successful and delivered more shareholder return.
- There's a lack of specificity and granularity in research databases, and there's room for important work on diversity, equity, and inclusion in retina.

Figure. Dr. Haller has been the ophthalmologist-in-chief at Wills Eye Hospital in Philadelphia since 2007, and her list of publications is nearing 500.

effect change. In that 2015 editorial, I looked around for examples of journals, even outside the field of medicine, that had made efforts to expand the number of women editorialists. When asked to nominate someone for a role, we usually think of our own friends and the people we know. Thus, to the extent that there have been fewer women and fewer people of color in the field, the existing hierarchy simply didn't know a diverse group of people to ask. It takes work and intentionality to expand who you know and who you might ask to achieve change.

It's encouraging that, when we identify and then measure differences, we can see the reasons for those differences and maybe advance the cause. Neil M. Bressler, MD, was the editor-in-chief of *JAMA Ophthalmology* at the time, and he invited me to write that editorial. Later, we did a study that looked at editorials written between 2015 and 2019, and there was a definite increase in the number of women editorialists.[2] That increase was led by *JAMA Ophthalmology*, and we have Dr. Bressler to thank because he really made an effort to include more women; it worked, and there was a ripple effect. Obviously, by that time, there were more women in senior positions, but it comes down to individuals and our responsibility to make the world a better place.

We conducted another study that looked at the presence of women on the podium—another instance in which speakers are chosen by their peers.[3] Between 2015 and 2019, there was not much of an increase, and it languished at about 20% to 25%. When we specifically looked at who was on the program committee, if there was at least one woman, there was significantly more representation. That's another way you can make a difference, but you must get women into leadership roles first.

When I took this job (Figure), there were only three women chairs in the entire country, and I was the only woman president of the American Society of Retina Specialists (ASRS) for 15 years until Judy E. Kim, MD, became the second in 2022. In eye journals, there are very few women on the editorial boards relative to men and, until recently, no female editors-in-chief.

We also looked at 25 years of retina publications, and we found a significant increase in women in first and senior authorship positions.[4] If there was a woman in a senior author position, it was much more likely to have a woman in the first author position. Leadership and mentorship are recurring themes that come up in all areas of diversity.

When we look across specialties, retina seems to be leading with DEI, so we can be proud of our specialty. If anything, we're punching a little above our weight.

Steve Sanislo, MD: Your approach to that research in 2015 was great because a lot of people were talking about the number of women in retina or ophthalmology, but they weren't specifically looking at leadership positions.

DR. SANISLO: WHAT ARE THE NEXT STEPS FOR YOUR RESEARCH?

Dr. Haller: We are interested in several things. When you talk about who's influential and who makes a difference, you cast a broader net. For example, Patel et al did an interesting study looking at the different relationships physicians can have with industry and who is considered worth engaging as an expert on scientific advisory boards and the like.[5] They found that women were significantly underrepresented across the board in those positions. That's one of the most apparent areas with disparities, and it may reflect the intersection between the disparities on the industry side and the disparities on the medical side. Even when women were involved, they were paid less.[5]

Another point is how DEI issues affect patient care, the way we recruit patients for clinical trials, and how we build a pipeline of retina specialists who are more representative of our patient base. We're increasingly understanding that having physicians whom you can relate to makes a difference no matter who we are.

I commend the ASRS for making an effort to have us all log in and put more in our online profiles about race and ethnicity so we can get more granularity, understand ourselves a little better, and maybe correlate it with other types of outcomes.

Rebecca Soares, MD, MPH, a past Wills Eye fellow, spearheaded some interesting work looking at AMD clinical trials and evaluating how the clinical trial sites affect patient access.[6] The study found that clinical trial access was reduced for Black, Hispanic, and Asian patients, and it correlated with education level. Highly educated patients have more access, just based on geography. All the benefits of participating in clinical trials accrue to more privileged patients and are meted out unequally.

We just did an IRIS database study of treatment in the

WHEN WE LOOK ACROSS SPECIALTIES, RETINA SEEMS TO BE LEADING WITH DEI, SO WE CAN BE PROUD OF OUR SPECIALTY. IF ANYTHING, WE'RE PUNCHING A LITTLE ABOVE OUR WEIGHT.

first year after central retinal vein occlusion (RVO) with a concurrent diagnosis of macular edema.[7] We found disparities in treatment across the United States, with women being treated less in the first year. We know that early treatment is important in terms of visual outcomes, and Black, Asian, and older patients were treated less, in addition to women. There was a VA sweet spot of 20/40 to 20/200 where about 75% of patients are treated. Even after all these years of available treatments for RVO, there's undertreatment and disparities, and you wonder why. Figuring that out and how to mitigate it—that's next!

Another interesting research avenue is the residency match, which didn't even record any information about race or ethnicity until 2016. If we wanted to look at all the Black retina specialists who've been trained to see whether there's less disparity in their RVO treatment—you can't do it because we don't have any data yet. The 2016 group is just finishing their training and going into practice right now, so we don't know what the outcomes are yet. We don't have good information about, for example, Hispanic or Asian ethnicity, either the patient or physician. There are so many things that we don't have the granularity to understand yet.

DR. SCOTT: THERE HAS BEEN SOME PUSHBACK AGAINST THE EXAMINATION OF DEI PRACTICES. IF YOU HAD TO SPEAK TO A COLLEAGUE WHO'S DESIGNING THE PROGRAM FOR A MAJOR MEETING, A PANEL, OR AN AD BOARD, WHAT WOULD YOUR ADVICE BE REGARDING THE IMPORTANCE OF DIVERSITY?

Dr. Haller: I share your dismay at what is a disastrous current climate that uses huge generalizations to disparage legitimate concerns about DEI. The best way to combat this is with data. It's a daunting environment, but at least in our professional community, data is the answer.

For example, researchers have looked at board diversity, the time spent deliberating on questions, and the type of decisions that were made, with metrics on the quality of the decisions and how much deliberation, research, and time was put into them.[8] If the board was diverse, it made a huge difference, which makes sense. If you're hanging out with your buddies from college, you may all come to the discussion with the same preconceptions.

But when I'm around a table of people I don't know, particularly if they come from different backgrounds, I do my homework because I want them to be impressed with my preparation. I'm coming in with a really different perspective. On more diverse boards, I push myself a little harder to prepare for the discussion, and that plays out in actual research and outcomes. Studies have looked at boards with more women and found that they've been more successful and delivered more shareholder return.[8] To combat the current antidiversity claims, we need to conform with language they understand and show them the data about outcomes in terms of the effectiveness of more diversity.

DR. SANISLO: IN LARGE CLINICAL TRIALS, WHY DO YOU THINK WE RARELY SEE ANY SUBGROUP ANALYSIS OF OUTCOMES BASED ON MALE VERSUS FEMALE?

Dr. Haller: I think it's because people haven't thought to do it. When Bernadine Healy became head of the National Institutes of Health, women weren't included in trials. The information about treating cardiovascular disease, for example, was all male centered. The classic heart attack was the *male* classic heart attack. Now we know that women have different symptoms than men, and the outcome was that women were being underdiagnosed and undertreated.

In our recent research on RVO, we found that women weren't treated as aggressively as men in the first year after diagnosis, and that was in all subgroups of visual acuity.[7] That delay and undertreatment must translate into worse outcomes, which is something we're interested in looking at now. Women have worse visual outcomes in terms of blindness all around the world. Is it because they're deprioritizing themselves and taking care of their family first, or is it because physicians don't treat them aggressively enough? There are likely many reasons that differ based on the culture. These are all very important questions.

DR. SCOTT: WHY DID YOU DECIDE TO BECOME A VITREORETINAL SURGEON, AND WHAT WAS THAT LIKE FOR YOU IN SUCH A MALE-DOMINATED FIELD AT THE TIME?

Dr. Haller: I came to ophthalmology loving surgery. I was a Halsted intern in surgery at Johns Hopkins and was all set to go into general surgery. I came down to Wilmer Eye Institute and spent a month with Stuart Fine, MD, during my fourth year of medical school. It was too late for the match, so I did a year of research in pathology with

Frederick A. Jakobiec, MD, DSc, and then matched into ophthalmology. What was attractive about ophthalmology for me was the surgical aspect, and in those days, if you were a woman, you had to have a male attending who would take you under his wing, unless you were very lucky to find one of the few female mentors around.

Dr. Fine was quite a recruiter of medical students into ophthalmology, and I was one of the many he introduced to the field. And then Ronald G. Michels, MD, considered the top retina surgeon in the world at the time, became a mentor; I wanted to be like him, too! When I was a first-year resident, my senior residents, Eugene De Juan, MD, and Paul Sternberg, MD, were both going into retina surgery, and they would get me to assist in the OR, and I couldn't believe it. During my first operations, I said, "Wow, you can do this? This is just awesome." Arnall Patz, MD, was a wonderful inspiration and support, and Morton F. Goldberg, MD, was hugely influential and gave me projects that allowed me to give some talks. Robert B. Welch, MD, was the first person I did scleral buckles with; he would tell me about Alice R. McPherson, MD, because she had been a fellow at Massachusetts Eye and Ear with him. He instilled in me a desire to be part of that world.

I aspired to emulate all these heroes, and it took me a while to find my own voice. When I became more confident just being myself, I had more success. I, like most women of my era, had mostly male mentors, and they were great.

FURTHER READING

Women in Vitreoretinal Meetings: 2015-2019
By Ali Syed, BS; Audina M. Berrocal, MD; and Jayanth Sridhar, MD

Diversity in Clinical Trials: A Work in Progress
By Abdul-Hadi Kaakour, MD, MS; Hong-Uyen Hua, MD; and Aleksandra Rachitskaya, MD

The Effect of Race on Vision: A Look at DME
By M. Ali Khan, MD, FACS

Exploring the Gender Gap Through Authorship in Retina
By Ankur Nahar, BS, and Julia A. Haller, MD

DR. SANISLO: WHAT ARE YOUR THOUGHTS ON RESEARCH REGARDING OTHER BIAS SUCH AS RACE OR SEXUAL ORIENTATION?

Dr. Haller: Ethnicity is particularly hard to study because of the missing data. In our IRIS RVO analysis, for example, we expected Hispanic ethnicity to have a negative correlation, but it didn't show up in our analysis; of course, we had about 30% with no ethnicity data.[7] When you don't have the data, you just don't know. We must make more of an effort to figure out what we want to be studying and then collect that data. Any subgroup that's been marginalized is probably hard to study with very little data, and low enrollment numbers.

For example, we looked to see if there was a difference in outcomes for Black patients treated with ranibizumab (Lucentis, Genentech/Roche) versus White patients, and there wasn't enough data due to few Black patients enrolled.[9] It looked like Black patients didn't do as well as White patients, but you couldn't be sure because there weren't enough patients enrolled at any one clinic. And that's the entire Genentech and DRCR Network database. We must correct this.

As another example, the 2023 AAO Jackson Memorial Lecture was a remarkably illuminating talk on disparities, where Eve J. Higginbotham, SM, MD, ML, made many important points, including pointing out the research into the huge genetic diversity within Africa, the descendants of whose people have been lumped together as *Black* in our studies because of a lack of awareness and the missing data.[10] There's a lack of specificity and granularity in our databases, and there's a lot of room for much-needed, interesting work.

DR. SCOTT: DO YOU HAVE ANY FINAL COMMENTS ABOUT WHERE WE ARE AS A FIELD CONCERNING DEI, AND HOW WE CAN KEEP MOVING THE FIELD FORWARD?

Dr. Haller: We have made progress. Fifteen years ago, none of the interviews I did were on this topic. I gave the first DEI talk at AAO retina subspecialty day only 2 or 3 years ago. So, we're late to the game, but it's on our radar now, and it needs to stay there. We now have explicit leadership training that we're doing in ophthalmology; it's important because everyone can be a better leader. And part of leadership training is learning how to harness a diverse workforce.

I must give a shout-out to our retina organizations and also Women in Ophthalmology. There was no society for women in ophthalmology or women in retina when I was coming along. And now those groups are specifically talking

(Continued on page 28)

A New Perspective on the Retina Wage Gap

The latest research on Medicare reimbursement patterns reveals ongoing disparities between male and female retina specialists.

By Aidan Gilson, BS, and Ron Adelman, MD, MPH, MBA, FARVO

The most recent Nobel Prize in economics was given to Claudia Goldin, PhD, the Henry Lee Professor of Economics at Harvard University, for her work identifying key drivers for gender differences within the labor market. She showed that the average woman in the United States earns only 80 cents on the dollar compared with the average man.[1] The field of health care is not immune to this disparity, considering that the Association of American Medical Colleges found that White male physicians earned more than women or men of color.[2] In the field of retina, significant disparities remain for female retina specialists.

THE STATE OF THE FIELD

We recently examined physicians' total annual payment through Medicare in 2020 and found that female retina specialists received only 65 cents on the dollar compared with their male counterparts (Figure 1).[3] This represents the conflation of many underlying factors that affect pay, such as patient volume, prevalence of female leadership and mentorship, funding opportunities, career advancement, and rates of female authorship. However, equally important are larger societal pressures for working women to sacrifice their careers for tasks related to childcare and other domestic responsibilities.[4]

Although Medicare reimbursement is not equivalent to take-home physician compensation, it offers a unique benefit when examining the wage gap, in that it is a nationally standardized system. Apart from some geographic variations, any physician who bills for CPT 67028, an intravitreal injection, will receive the same standardized reimbursement in the same geographic area. This affords researchers a unique opportunity to examine disparities with minimal confounding factors, such as salaries that are negotiated on a case-by-case basis.

Our study found that the greatest identifiable contributor to the inequity in Medicare reimbursement is the difference in the average number of patients seen by male and female retina specialists.[3] When controlling for the number of patients seen by female retina specialists, the disparity lessens to 89 cents on the dollar (Figure 2).

AT A GLANCE

- In 2020, female retina specialists received only 65 cents on the dollar in total annual payment through Medicare compared with male retina specialists.
- Both married female physicians and female physicians with children work, on average, fewer hours than the respective male physician population.
- The extra time female physicians spend with patients can lead to increased rates of preventive care, lower patient volume, and higher patient-reported experiences of empathy from their care provider.
- We must always be careful when examining multifactorial issues such as gender inequity because an oversimplification of the causes and outcomes can be misleading.

Figure 1. In 2020, female retina specialists received only 65 cents on the dollar in total annual payment through Medicare compared with their male counterparts.[3]

Figure 2. When controlling for the number of patients seen, the Medicare reimbursement increased to 89 cents on the dollar for female versus male physicians.[3]

Although this finding provides a path for intervention, it also makes us question why there is such a significant gap in the first place.

One of Dr. Goldin's points in her work was that the pay gap would increase after a woman has her first child, which could lead to a decrease in hours worked and patients seen. This assumption could extend to physicians, because unmarried physicians work the same amount regardless of their gender, but both married female physicians and female physicians with children work, on average, fewer hours than the respective male physician population.[5,6] However, this reduction would be expected to occur only in a smaller window when children are younger. Unfortunately, there is limited evidence that the reimbursement disparity decreases at specific timepoints of life. The inequity between attending physicians in their first years after fellowship continues through 25 years of experience, and all stages in between.

Although family responsibilities (traditionally—albeit unduly—placed on women) affect the hours worked, they do not completely explain the wage gap.

Factors that affect how many patients a physician sees are not unique to ophthalmology. Female physicians, regardless of specialty, spend more time, on average, with each patient than male physicians.[7] Some research suggests this may be related to differing patient expectations, with the assumption that female providers should spend more time with patients compared with male providers.[8,9] As physician compensation is often directly linked to the throughput of services provided, spending more time with each patient can have negative effects on a female provider's total compensation.

However, research shows that the extra time that female physicians spend with patients can lead to increased rates of preventive care, lower patient volume, and higher patient-reported experiences of empathy from their care provider—all of which contribute to lower rates of litigation for female versus male physicians.[10,11] Thus,

THE GREATEST IDENTIFIABLE CONTRIBUTOR TO THE INEQUITY IN MEDICARE REIMBURSEMENT IS THE DIFFERENCE IN THE AVERAGE NUMBER OF PATIENTS SEEN BY MALE AND FEMALE RETINA SPECIALISTS.

female retina specialists are compensated at a lower rate, despite providing exceptional patient care.

Many other factors can lead to decreased patient volume, including different referral rates between male and female retina specialists. For each patient, female ophthalmologists may perform fewer procedures, perform procedures that are compensated less, or code clinic visits differently, leading to reduced reimbursement for equivalent work. For example, a level 2 visit is often reimbursed the same by the same insurance; however, if a female ophthalmologist elects to code a 21-minute visit as an 18-minute one, she will receive lower reimbursement.

FUTURE EFFORTS

We must always be careful when examining multifactorial issues such as gender inequity because

an oversimplification of the causes and outcomes can be misleading. Were the conversation to end at the explanation that reimbursement disparities are due to differences in patient volume, an incorrect conclusion may be that female physicians are receiving less compensation because they aren't working as hard. This could not be further from the truth.

Decreased patient volumes for female retina specialists is a complex issue with multiple underlying factors. A disparity in Medicare reimbursement is just a symptom of an underlying inequity.

In 2020, only 17% of practicing retina specialists were women.[12] Less than 30% of first or last authors in retina publications are women.[13] Female ophthalmologists receive less national funding and are less likely to be represented in senior academic positions.[14,15]

The wage gap is just one piece of a very large puzzle. Hopefully, further research will reveal other factors so that we can adequately address these issues. ■

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(Continued from page 25)

about leadership, mentoring, and even spearheading studies and piloting projects.

The other message for young trainees is to get the best training possible, and work hard to be excellent physicians and surgeons. That's the foundation for leading.

There are many more options out there for mentoring and leadership training, and people can aspire to that on every level, be it local advocacy, subspecialty groups, the AAO's Young Ophthalmology group, and all the way to the top. There are many opportunities out there, and I'm very encouraged by this generation of trainees.

We can be proud of the outstanding students who want to go into our specialty. There's a lot of hope there. ■

Editor's note: This manuscript has been edited from the original transcript for clarity and space purposes.

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Improving the Retina Fellowship Applicant Pool

How can we prioritize diversity and inclusion in retina from the very beginning?

By Kirsten Simmons, MD, MHSc, and Nita Valikodath, MD, MS

Ophthalmic advancement, patient-centered care, and outreach are contingent on sustained efforts that recruit and retain a diverse workforce within our dynamic specialty.

WHERE WE STAND

The Association of American Medical Colleges (AAMC) defines *underrepresented in medicine (URiM)* as "those racial and ethnic populations that are underrepresented in the medical profession relative to their numbers in the general population."[1] While this definition allows for routine accommodations based on changing ethnic populations within our country, the groups to whom this definition most commonly applies to are Blacks, Hispanics, Native Americans (American Indian/Alaska Native/Native Hawaiian), and mainland Puerto Ricans.[1,2]

Decades of ophthalmic research has demonstrated vast examples of disease-specific disparities in treatment and outcomes based on race/ethnicity, socioeconomic status, and other factors.[3] Importantly, physician-patient concordance in demographic factors (eg, race/ethnicity, culture, and gender) increases patient satisfaction, medical adherence, and health outcomes.[4-6] However, women comprise approximately half of the medical student population yet make up 22% to 54% of surgical residents and fellows across subspecialties.[7] Similarly, URiMs comprise 7.7% of resident trainees, 6% of practicing ophthalmologists, and 5.7% of ophthalmology faculty, despite making up 30.7% of the US population.[8]

By lacking in diversity, ophthalmology misses out on the wealth of knowledge and experiences embodied within women and URiM trainees that can help tackle complex research and clinical challenges, coined the *diversity bonus* by social scientist Scott E. Page, PhD.[9]

AN UNEQUAL EDUCATION SYSTEM

Nearly 70 years after the landmark 1954 Brown vs. Board of Education Supreme Court ruling, our country's education system continues to perpetuate unequal learning opportunities. There is a stark opportunity gap between Black and White students (known as the *achievement gap*).[10,11] Black students are more likely to attend schools with less funding per student, have less access to advanced placement courses, have lower rates of acceptance into gifted programs, experience lower expectations from teachers, and receive greater suspensions and discipline.[12-14]

Although we cannot uproot decades of inequitable education, we can acknowledge its existence. Ophthalmologists in a position of influence must examine

AT A GLANCE

- Women comprise about half of the medical student population yet make up 22% to 54% of surgical residents and fellows across subspecialties.
- Residency program directors and selection committee members should implement a holistic application review and selection process to improve the match for underrepresented-in-medicine applicants into our field.
- Mentorship programs create mentor-mentee partnerships and support opportunities for junior residents to present at national conferences.

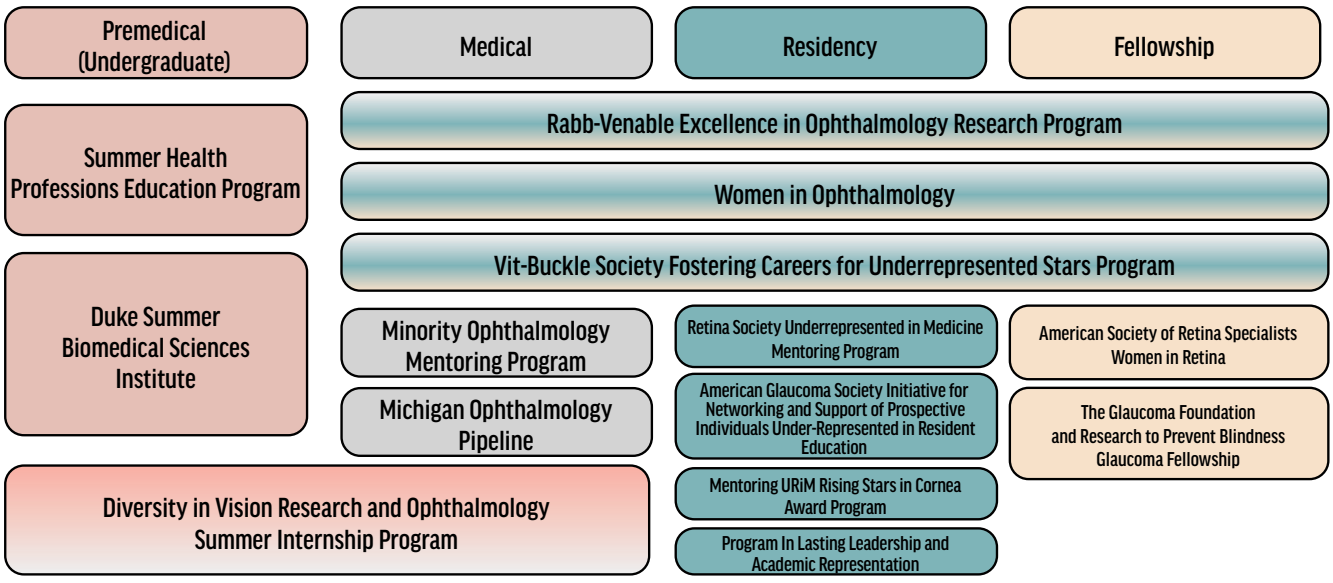

Figure. These pipeline programs for URiMs in ophthalmology and ophthalmology subspecialties continue to help us achieve a diverse ophthalmic workforce. While this list is not exhaustive, we applaud the ongoing work across numerous medical schools, trainee hospitals, and health care societies to further this mission.

each step of the student-to-physician pipeline to develop sustainable programs and policies that will increase awareness of our specialty, offer academic and research support, promote holistic evaluations, and prioritize longitudinal career development and retention.

UNDERGRADUATE AND GRADUATE TRAINING

It is imperative that URiM students establish an ophthalmology mentor early in their educational training. Health expos, career exploration days, and youth summits are invaluable because they can impress upon young learners that a career in ophthalmology is real and attainable.

At the collegiate level, we must recognize the valuable role that Historically Black Colleges and Universities (HBCUs) play in the student-to-physician pipeline; they educate 10% of all Black undergraduates, accounting for 17% of bachelor degrees and 24% of STEM field degrees earned by Black students.[15] Many minority patients still find the greatest amount of trust and reliability in the medical centers that are associated with or predominantly staffed by members of their own community. Without a doubt, partnership with HBCUs is integral to meeting the demand of diversifying our field with bright and culturally competent physicians.

Linz et al performed a cross-sectional survey of the reasons why medical students (particularly URiMs) chose not to pursue a career in ophthalmology.[16] Regardless of URiM status or gender, the top reasons included insufficient interest and lack of exposure. A greater percentage of URiMs, however, responded that ophthalmology had insufficient role models or mentorship opportunities. This same group expressed "concern for finding same-race or same-gender role models/mentors in this field" and "concern about the lack of ethnic/racial diversity in the field."[16]

POST-GRADUATE TRAINING AND FACULTY

Residency program directors and selection committees hold one of the most powerful positions to transform the diverse landscape of our field. We suggest two strategies to aid significantly in matching URiMs into our field.

First, directors and committee members should be aware of their personal biases (one tool is the Harvard Implicit Association Test[17]) and work to actively deconstruct them.

Second, committees should implement a holistic application review and selection process, which is particularly important given the fact that overreliance on the United States Medical Licensing Examination scores can eliminate many URiM applicants from review.[18]

A 2022 cross-sectional study found that among all medical disciplines, ophthalmology has the second lowest number of URiM residents.[19] The 8-year study (2011-2019) did not observe a positive trend of URiMs entering surgical specialties but did see a positive trend with non-surgical specialties. Still, we are encouraged to see an annual increase in the percentage of Black medical students who successfully matched between 2020 and 2022.[20] This milestone would not have been possible without the efforts of pipeline programs such as the AAO's Minority Ophthalmology Mentoring Program and the Rabb-Venable Excellence in Ophthalmology Research Program, the latter of which held an outstanding match rate of 75% between 2008 and 2020.[21]

Women and URiMs continue to be underrepresented across surgical fields. Choinski et al examined surgical fellow application demographics in 2018 and found that women constituted 26% to 54% of applicants (lowest in thoracic surgery and highest in pediatrics). URiMs accounted for 9% to 15% of applicants (lowest in colorectal surgery and highest in pediatrics).[7]

Ali et al completed one of the first studies investigating the sex and racial disparities among ophthalmology subspecialty fellowship applicants. Pediatric ophthalmology had the highest percentage of matched applicants who were women, while vitreoretinal surgery had the highest percentage of men. URiMs, who represented 8.8% of all matched fellows, had a lower match rate (55%) compared with their non-URiM counterparts (72.2%).[22] In addition, underrepresented applicants had a lower median of 10 submitted applications for fellowship compared with Asian and White applicants (21 and 17, respectively). One potential reason for this discrepancy is the financial barrier. On multivariable analysis, there were higher odds of matching into fellowship with more completed interviews and a higher Step 2 CK score.[22]

A lack of diversity among premedical students leads to a lack of diversity in medical school training, residency, fellowship, and faculty. Fairless et al analyzed the 2019 AAMC faculty roster and found that ophthalmology had only eight URiM chairpersons and the third lowest proportion of URiM faculty compared with 17 other clinical departments.[23] While the proportion of URiMs entering medical school has increased, this has not translated into the recruitment, retention, and equitable promotion of URiM faculty members and chairpersons across many specialties, including ophthalmology.[24] The potentially taxing experience of a URiM faculty member without career development, mentor support, and perception of inclusion and equity should not be ignored.[25] As URiM trainees consider the pursuit of further training, one determining factor may be how a particular subspecialty and future department will support their professional growth.

MENTORSHIP PROGRAMS

Pipeline programs are crucial in a trainee's career trajectory (Figure). Mentorship programs can provide surgical simulations, create mentoring partnerships, and support opportunities for junior residents to present at national conferences. For example, the Vit-Buckle Society developed the Fostering Careers for Underrepresented Stars program, an initiative designed to expose URiMs to surgical retina alongside junior and senior faculty mentors. The Retina Society established its Underrepresented in Medicine Mentoring Program, which provides mentor-mentee partnering for the development of research projects and subsequent publication.

Women in Ophthalmology provides an annual mentor-mentee match for residents interested in a subspeciality. With this program, trainees can gain gender-congruent advice on important topics such as work-life balance, leadership, and how to navigate male-dominated organizations.

The Program in Lasting Leadership and Academic Representation, supported by the Byers Eye Institute and the Rabb-Venable Excellence in Ophthalmology Program, is geared toward the recruitment of URiMs into academic ophthalmology. The program provides interactive panels on various topics, such as how to become future program leaders, apply for career development awards, and build partnerships with medical device and pharmaceutical companies.

Industry partners have also developed career development awards to support junior URiM faculty within academic medicine. For example, the Genentech Career Development Award for Underrepresented Minority Emerging Vision Scientists provides monetary support and mentorship outside of the recipient's home institution.

WHY IT MATTERS

It behooves us to invest our resources and time in all stages of the student-to-physician pipeline; in doing so, we will increase the diversity of our subspecialty fellowship applicants and academic faculty. ■

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Addressing Health Disparities in The Real World

Lessons Learned From AI

Novel metrics can help clinicians better understand—and alleviate—bias in technology and clinical encounters.

By Michael D. Abramoff, MD, PhD

Improving health equity has become a driving force within the medical community, US Congress, and the Department of Health and Human Services, and is even starting to affect reimbursement.[1] While there are many reasons for avoidable health inequities, lack of equitable access to diagnosis and treatment are prominent in disease states ranging from breast cancer to depression and diabetic eye disease.[2-7] Currently, fostering health equity is a goal of all health care stakeholders: patients, providers, ethicists, payors, regulators, legislators, and even AI creators.

Autonomous AI—where the medical decision is made by the AI without human oversight or clinician input—has received broad stakeholder support, including from retina specialists, considering the first device cleared by the FDA provides a diabetic retina examination.[8] Where rigorously validated and appropriately implemented in real-world clinic workflows, AI tools can improve clinician productivity, health equity and efficacy, and clinical outcomes, all while reducing cost.[9-13]

THE PROBLEM

When first encountering autonomous AI, clinicians raised many concerns, including job loss, potential bias, and the effect on health equity, even though such issues already affect non-AI-related health care processes and interactions.[14] This is especially true when the autonomous AI (eg, LumineticsCore, Digital Diagnostics) claims that it is intentionally designed to improve access, outcomes, and health equity for underserved populations—and paves the way, ethically, for other autonomous AI systems on the market.

Such concerns have led to an explosion of studies on the risks and benefits of AI and how to address them. In response, we and others created an ethical framework for AI as the foundation upon which autonomous AI regulation and AI reimbursement is built.[13,15,16]

Provider concerns of bias, patient benefit, cost, liability, and effect on health equity led to the reexamination, from an ethics perspective, of all health care interactions and processes, even those performed solely or mostly by specialists. Using our ethical framework as a foundation, we, together with the FDA and other health care stakeholders, recently completed a careful analysis of how

AT A GLANCE

- When first encountering autonomous AI, clinicians raised many concerns, including job loss, potential bias, and the effect on health equity.
- With AI, the creators can measure how much each bioethical principle is being met through the principle of metrics for ethics.
- The goal of any analysis is to provide transparency about potential sources of bias and health inequity, and the sustainability of mitigation efforts.

bias can be introduced—and mitigated and addressed—during the conceptualization, design, engineering, training, deployment, regulation, and monitoring of AI in the real world, and it easily translates to any health care process.[17]

MEASURING ETHICS

The three central bioethical principles are beneficence/maleficence (patient benefit or "do no harm"), justice (ie, equity), and autonomy (Figure).[18] Any provider, medical process, or treatment is unable to meet each bioethical principle fully. Rather, everything requires a balance between each ethical principle. For example, maximizing outcomes for lung cancer (beneficence) may be reached by banning smoking, which negatively affects the bioethical principle of patient autonomy.[15]

With AI, the creators can measure how much each bioethical principle is being met through the principle of *metrics for ethics*.[16] For example, we (with the FDA) created metrics for measuring bias in AI algorithms and the effect on a given population. One example is the concept of *population-achieved sensitivity*, which measures how many patients a diagnostic autonomous AI can identify in an entire population. If an AI system is highly sensitive but works only on a small subset of patients, the population-achieved sensitivity will be lower compared with an autonomous AI system that works for the majority of the population but has a slightly lower sensitivity—more of the total number of true cases are identified.

ETHICS IN HEALTH CARE

Any given health care process can improve outcomes for a patient or an entire population, thereby maximizing the bioethical principle of beneficence. If this assumed improvement is not evenly distributed across the patient group or population, the bioethical principle of justice (ie, equity) is negatively affected, and health inequity is the result. When stakeholders within the health care system take a more active role in allocation to improve beneficence, justice, or both, the bioethical principle of autonomy may be infringed upon. The trick is finding a balance between the three principles.

Bias in any part of the health care process may lead to inequity and, in the past, has resulted in poorer health outcomes for specific underrepresented, underserved, and underresourced groups.[19,20]

For example, a recent study found that providers' charts documented Black patients' symptoms and signs in a more pejorative manner,[21] which has the potential to exacerbate health disparities. Other studies suggest physician bias in caring for other populations as well.[22-24] In retina, a recent study showed that reading center confidence in evaluating fundus images for diabetic eye disease was lower in more pigmented retinas.[25]

Such bias in clinical practice reduces the bioethical principle of justice as described by Char et al and Abramoff et al.[15,16] Using the metrics for ethics, bias and its effect on beneficence and justice can be quantified to better understand the differential effect of a health care process on a particular group.

IMPROVING ETHICS IN PRACTICE

To mitigate health care bias, we can apply our ethical AI framework to our daily practice as retina specialists. To start, we can translate the AI creation phases into descriptions relevant to clinical practice as follows:

- Conception: target disease and population
- Design: management and treatment (ie, how we choose to treat the disease)
- Development and validation: clinical training
- Access and marketing: practice characteristics
- Monitoring: follow-up and reporting

Using this approach, we can analyze the potential bias in each of these aspects; we can also assess the potential mitigation strategies, although the capability of the individual retina specialist to affect these may vary. The primary goal of such analysis is to provide transparency about potential sources of bias and health inequity, and the sustainability of any mitigation based on the financial and time resource constraints that must be adequately balanced.

Target disease and population. *Invisible populations* are the often-large segments of the population that are underrepresented, underserved, underresourced, and rarely or never get proper eye care. For example, only 15.3% of adults with diabetes who are recommended to get an annual examination actually get it.[26] This means that more than 80% of Americans are *invisible* in this regard, and this is the case with many, especially chronic, eye diseases. Typically, these invisible populations are underrepresented in (phase 3) clinical trials validating new treatments, limiting our ability to understand their efficacy, if any, in these patients. Mitigating such bias is a primary concern in the design and evaluation of clinical trials, and not so much something that the individual specialist can control.

Management and treatment. Mitigating potential bias in the efficacy of any given therapy for certain culturally, genetically, or otherwise characterized subgroups is another concern for those engineering the therapies themselves, not necessarily individual practitioners.

Clinical training. Medical school, residency, fellowship, and exposure to various populations can exacerbate or mitigate bias when dealing with patients in these populations. For example, during a study of children with diabetes, my colleagues and I found anecdotal evidence that diabetic eye disease may manifest differently in young patients. Although this is now the subject of further research, the current literature pertaining to diabetic eye disease in the

Figure. Physicians must always strive to find the best balance between the three central bioethical principles of beneficence/maleficence, justice, and autonomy.

pediatric population is lacking—a clear example of age bias. As another example, learning how to diagnose retinal disease in eyes with various levels of retinal pigmentation or different amounts of pupil dilation can limit unconscious bias in clinic and allow better care across many populations.

Practice characteristics. Where we decide to practice, and which populations we see (often decided by which payer contracts we engage in), can introduce bias.

Monitoring. Reporting in systems such as the AAO's IRIS registry itself can be influenced by the populations in which we practice and how we treat and manage our patients. Such a bias in the registry can be mitigated by ensuring diversity among practitioners.

FROM AI TO CLINICAL PRACTICE

There are many sources of bias in clinical practice that have the potential to affect health equity, and they can be analyzed using our AI framework. Improving health equity starts with awareness. The good thing is that the bias that creates invisible populations can be addressed directly through highly scalable autonomous AI diagnostics, turning them into visible populations and providing them much-needed specialized retina care.[10] ■

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When Sex Becomes Relevant in the Retina Clinic

Three cases illustrate why a thorough history may preserve a patient's vision.

By Camiel J. F. Boon, MD, PhD, FEBO; Shravan V. Savant, MD; Justin D. Pennington, MD; and Sruthi Arepalli, MD

Retina specialists are keenly aware that systemic therapies and certain lifestyle choices can have ocular complications. But the same can't be said for patients. Many might omit certain medications from the intake form or fail to mention relevant experiences during the appointment—particularly when it has to do with gender identity or sexual preferences.

However, a patient's sexual activity *can* be relevant in an ophthalmic setting. Sexually transmitted diseases (STDs) can land a patient in the retina clinic with choroidal lesions, retinal hemorrhages, various forms of retinopathy, and retinal pigment epithelium atrophy, to name only a few.[1-5]

In addition, recent case reports of retinal manifestations related to hormone replacement therapy have emerged, linking the treatment with branch retinal vein occlusion, idiopathic intracranial hypertension, central serous chorioretinopathy (CSC), and optic neuropathy.[6,7] While the authors were unable to prove a cause-and-effect association, they emphasized the importance of awareness in patients undergoing this therapy.[7] Even excessive use of medications to treat erectile dysfunction can have long-lasting ocular effects.[8,9]

If a patient doesn't fit the typical demographic for their retinal findings, clinicians must ask challenging questions. Doing so might reveal an STD or systemic therapy for hormone imbalance, menopause, or gender-affirming care. Here, clinicians share three cases for which a patient's sexual history was the key to an appropriate diagnosis.

CASE NO. 1: DONUT VISION

By Camiel J. F. Boon, MD, PhD, FEBO

A 30-year-old man presented to an ophthalmologist with marked visual disturbances. When he woke up that morning, he felt as if he were looking through a gray donut with poor central vision related to a blueish discoloration. He also noted reduced vision and tunnel vision when reading.

He was sent to my clinic the next day, with a referral note listing his BCVA as 25/20 OU with a central roundish

AT A GLANCE

- A patient's sexual activity can be clinically relevant when it comes to sexually transmitted diseases, hormone replacement therapy, or sildenafil citrate (Viagra, Pfizer) use.
- Case reports of retinal manifestations related to hormone replacement therapy have emerged, linking the treatment with branch retinal vein occlusion, idiopathic intracranial hypertension, central serous chorioretinopathy, and optic neuropathy.
- If a patient doesn't fit the typical demographic for their retinal findings, clinicians must revisit the review of systems and ask challenging questions.
- Sildenafil citrate, a common medication to treat erectile dysfunction, can lead to retinal toxicity at high doses.

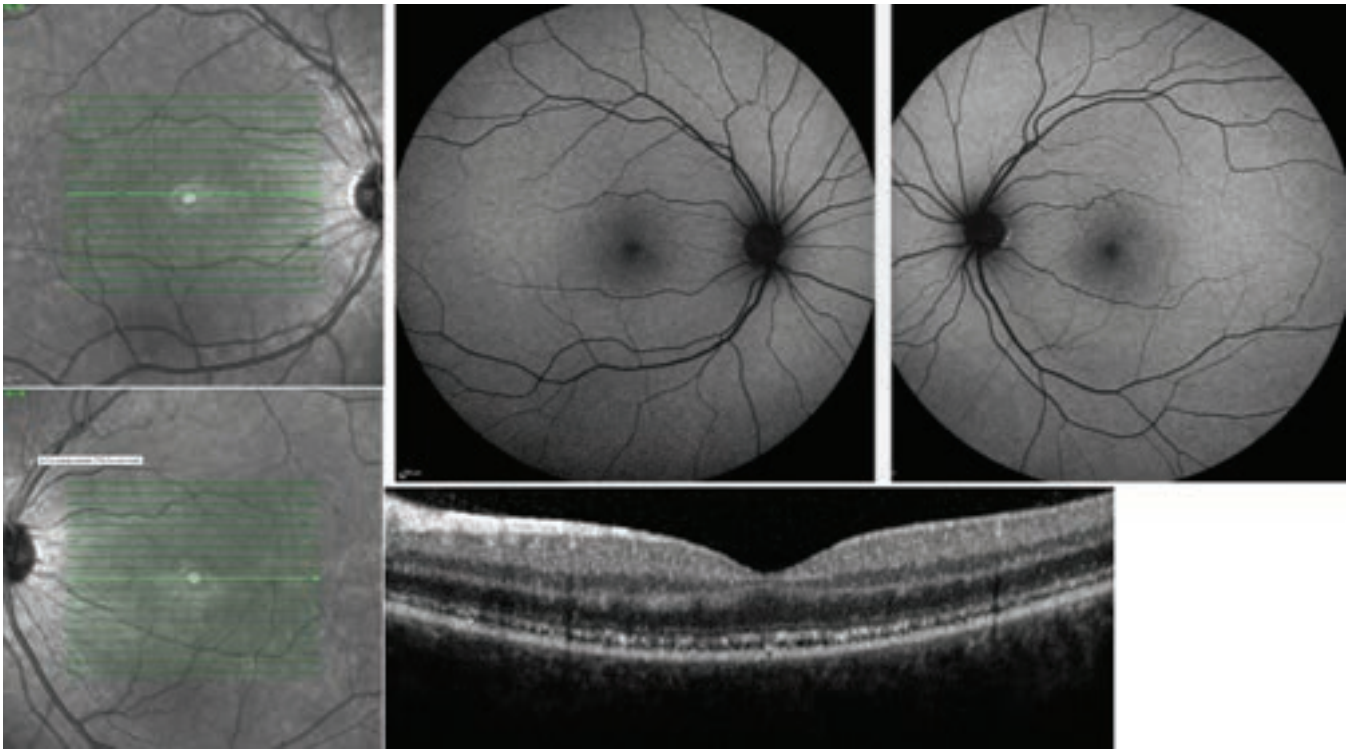

Figure 1. Although the patient's fundus autofluorescence imaging was normal, a granular irregularity to the ellipsoid zone was noted on OCT imaging.

lesion seen in the macula with no cells. The patient's systemic history was remarkable for childhood leukemia, for which he had been treated with chemotherapy.

Fundus autofluorescence imaging was normal, but OCT imaging showed a granular irregularity of the ellipsoid zone (Figure 1). The full-field ERG was normal with amplitudes within normal range in each eye. Color vision was near normal with no discernable pattern, and his visual fields showed a pericentral ring scotoma.

With little to go on for a diagnosis, I revisited the patient's social history. He admitted that the night before his symptoms arose, he had consumed several glasses of wine and had taken approximately 20 pills of 100 mg sildenafil citrate (Viagra, Pfizer).

The patient's symptoms improved gradually over several months of follow-up. At 2 months, the donut-shaped scotoma had resolved, and by 5 months, the patient said his photophobia had dissipated but that he still had issues with adaptation to changes in light. The OCT scan still showed some residual granular irregularity of the ellipsoid layer.

Discussion

Sildenafil citrate, a common medication to treat erectile dysfunction, can lead to retinal toxicity at high doses.[8-10] Sildenafil is a phosphodiesterase type 5 inhibitor, which increases cyclic guanosine monophosphate, leading to an increase in photocurrent duration and light sensitivity.[11] Similar to the patient discussed here, another case report by Yanoga et al found cone photoreceptor damage, demonstrated by ERG, OCT, and adaptive optics imaging, in a 31-year-old man with a history of taking a high dose of liquid sildenafil citrate.[9]

A careful patient history helped elucidate this patient's underlying condition, and his visual symptoms slowly resolved with long-term follow-up.

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CASE NO. 2: LIGHTNING BOLTS AND LESIONS

By Shravan V. Savant, MD, and Justin D. Pennington, MD

A 41-year-old man presented with a 4-day history of scintillations and "lightning bolt" photopsia in each eye. On review of systems, the patient had a history of abdominal pain, transaminitis, and a macular rash along his chest and abdomen 3 months prior to presentation.

His VA was 20/20 OU with IOP of 13 mm Hg OD and 10 mm Hg OS. There was no afferent pupillary defect, and the anterior segment was unremarkable. The dilated fundus examination revealed +1 vitreous cell and diffuse punctate white retinal lesions in each eye. Retinal imaging showed diffuse punctate hyperfluorescent lesions throughout the macula and midperiphery (Figure 2).

Comprehensive infectious and inflammatory lab testing and screening was performed. Syphilis serology

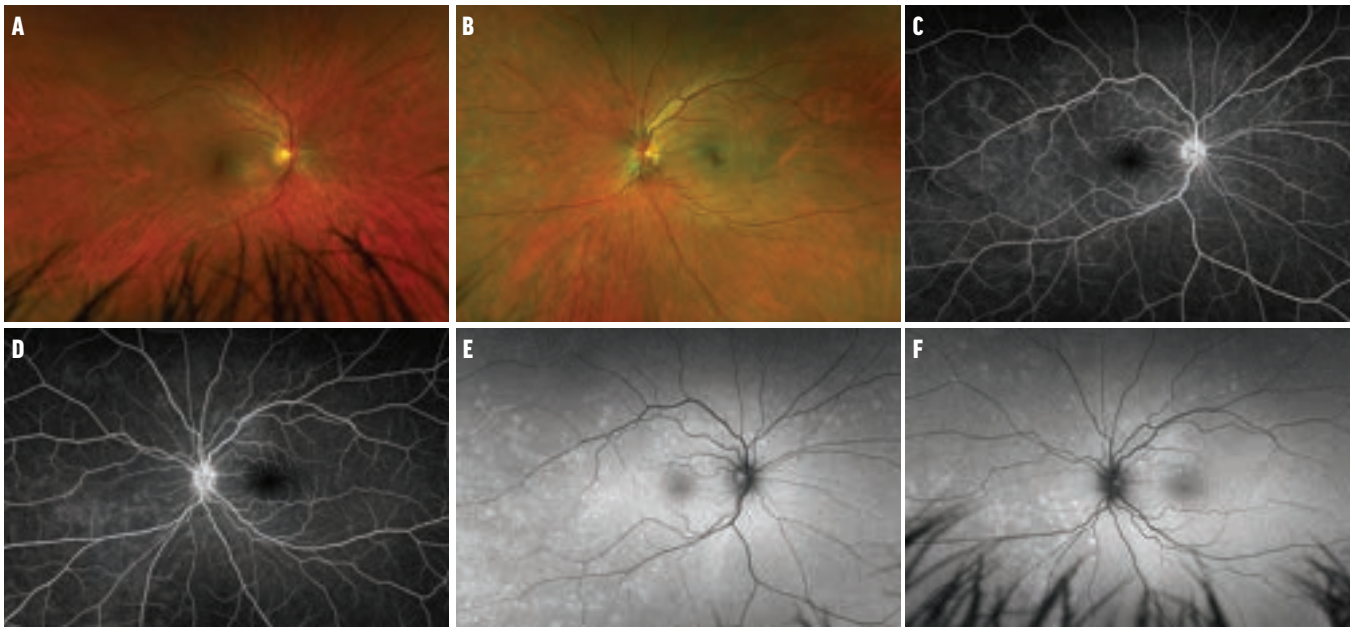

Figure 2. On dilated fundus examination, there was +1 vitreous cell and diffuse punctate white retinal lesions in each eye (A, B). Fluorescein angiography (C, D) and fundus autofluorescence imaging (E, F) revealed diffuse punctate hyperfluorescent lesions throughout the macula and midperiphery of each eye.

AS UNCOMFORTABLE AS IT MAY BE, CLINICIANS MUST TAKE A THOROUGH PATIENT HISTORY, INCLUDING A SOCIAL HISTORY, TO UNCOVER POTENTIAL UNDERLYING CAUSES OF RETINAL COMPLICATIONS AND RELATED SYSTEMIC SYMPTOMS.

(ie, fluorescent treponemal antibody [FTA] and rapid plasma regain [RPR] titer) was positive, indicating active syphilis infection. The patient was diagnosed with syphilitic posterior uveitis with retinitis and was referred to our infectious disease department. He received intravenous penicillin for 10 days and noted resolution of his visual symptoms.

Discussion

We postulate this patient had an early and mild presentation of acute posterior placoid chorioretinopathy because the lesions had not yet coalesced into true characteristic plaques. Rather, it presented as a pseudo-white dot syndrome, consistent with syphilis being one of the "great masqueraders."

Syphilis classically progresses through three stages: primary, secondary, and tertiary. The primary stage has a painless lesion or *chancre* at the site of infection. The infection can then disseminate and present as a secondary maculopapular rash within 1 to 3 months, followed by the tertiary stage. The tertiary stage presents over a wide timeline and includes granulomatous lesions, cardiac symptoms, and neurologic complications, including ocular inflammation. The current diagnostic workflow prioritizes the specific treponemal assays (ie, FTA) for a formal diagnosis and RPR as a secondary confirmatory test and an indicator of disease activity.[12,13]

CASE NO. 3: BLAST FROM THE PAST

By Sruthi Arepalli, MD

A 51-year-old man presented for a second opinion regarding his decreased vision and bilateral central scotomas. He stated that he was diagnosed with CSC at another office. VA was 20/100 OU, and the anterior segment examination was unremarkable. Posterior examination of the right eye showed an area temporal to the macula with subretinal fluid, which appeared hyperautofluorescent on autofluorescence. (Figure 3). OCT

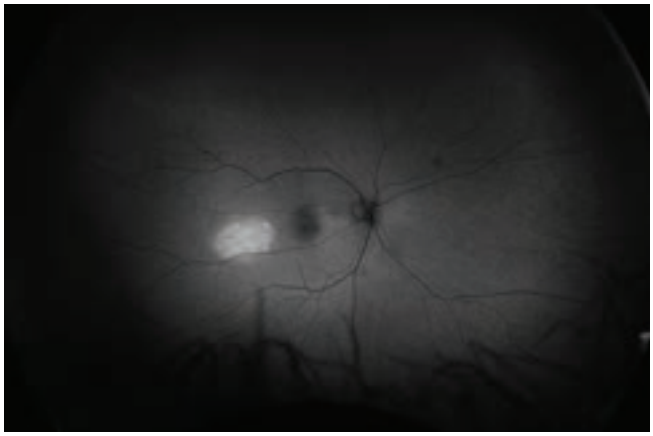

Figure 3. The subretinal fluid temporal to the macula appeared hyperautofluorescent on fundus autofluorescence.

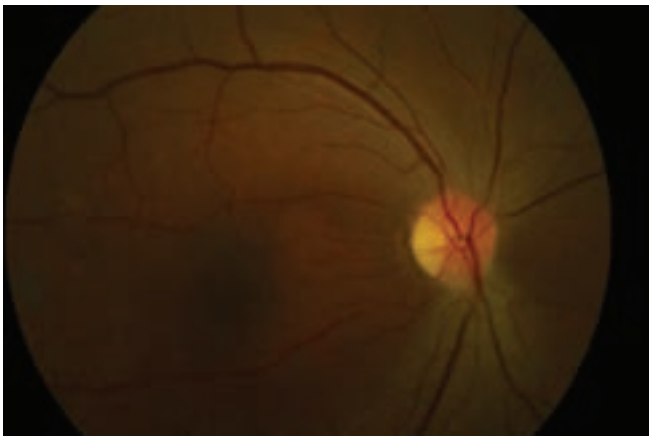

Figure 4. The temporal optic nerve pallor, seen here in the right eye, was also present in the left eye.

of the macula showed slight changes in the ellipsoid zone in each eye. Fundus examination showed temporal optic nerve pallor in each eye (Figure 4).

Given the eccentric location of the CSC and relatively preserved ellipsoid zone in each eye, I suspected that the decreased vision was not secondary to the macular changes. With the combination of ellipsoid zone changes and optic nerve pallor, I entertained the diagnosis of syphilis and asked the patient about high-risk sexual behaviors. The patient endorsed a history of unprotected intercourse while traveling abroad years ago. Subsequently, a brain MRI showed a right parietooccipital arachnoid cyst, which was not felt to explain the disc pallor. An MRI of the orbits showed bilateral optic atrophy without acute pathology. Lab work showed normal B1 and B12 vitamin levels, methylmalonic acid, folate, and homocysteine levels. However, syphilis IgM/IgG was positive, and RPR levels were elevated.

The patient was sent to infectious disease and treated with intravenous penicillin; however, his vision did not improve given the optic atrophy.

Ultimately, while the patient did have signs of CSC, a careful investigation into his high-risk exposures and lab work revealed a history of untreated neuro-syphilis.

ASK THE RIGHT QUESTIONS

As uncomfortable as it may be, clinicians must take a thorough patient history, including a social history, to uncover potential underlying causes of retinal complications and related systemic symptoms. Hormone replacement therapy, erectile dysfunction treatment, and sexual activity might not feel relevant to a patient seeking eye care, but retina specialists know otherwise. ■

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CONDITIONAL SURVIVAL OF PATIENTS WITH UVEAL MELANOMA

Factoring in years of metastasis-free survival may lead to an improved prognosis.

BY HARRISON S. FELLHEIMER, BA; MADISON M. WOODS, BA; JOSEPH D. DESIMONE, BS; AND CAROL L. SHIELDS, MD

Uveal melanoma is a rare, life-threatening malignancy that leads to systemic metastasis by 10 years in approximately 25% to 40% of patients.[1,2] Until recently, prognostication has relied on *nonconditional analysis*, a static method that estimates survival based on the time of diagnosis. One limitation of this method is that it cannot be used to estimate the prognosis of patients who have accrued a certain number of metastasis-free years since their initial diagnosis. In contrast, *conditional analysis* accounts for the increased survival probability that comes with accrued years of survival and, thus, can provide patients with a better idea of future risk.

In this overview, we explore three studies that use both conditional and nonconditional analyses and discuss how these analytical methods influence disease prognostication.

METASTASIS-FREE SURVIVAL AND FUTURE RISK

Zabor et al reported on the conditional and nonconditional metastasis-free survival of 6,863 patients with uveal melanoma 5 and 10 years after diagnosis using the online Surveillance, Epidemiology, and End Results database (Table).[3] These data highlight that conditional survival estimates of uveal melanoma improve with time from primary diagnosis to provide the patient with more personalized prognostic information.

Relevance of TCGA Group

Conditional survival analysis can also be calculated for cytogenetic variations. The Cancer Genome Atlas (TCGA) serves as a four-category prognostic classification for uveal melanoma metastatic risk based on the tumor's genetic profile. Using this classification, uveal melanoma is classified into Group A (disomy 3, disomy 8), Group B (disomy 3, 8q gain), Group C (monosomy 3, 8q gain possible), and Group D (monosomy 3, 8q gain multiple).[4]

Shields et al studied nonconditional and conditional metastatic rates in patients with uveal melanoma

TABLE. ESTIMATES OF NONCONDITIONAL AND CONDITIONAL METASTASIS-FREE SURVIVAL OF UVEAL MELANOMA AT SPECIFIC TIMEPOINTS

Years Since Diagnosis	Nonconditional Metastasis-Free Survival at 5 Years	Nonconditional Metastasis-Free Survival at 10 Years
0	80% (79%-81%)	69% (68%-71%)
Number of Years With No Metastasis	**Conditional Metastasis-Free Survival at 5 Years**	**Conditional Metastasis-Free Survival at 10 Years**
1	82% (81%-83%)	
2	87% (86%-87%)	
3	92% (91%-92%)	
4	96% (95%-96%)	
5		87% (85%-88%)
6		90% (89%-91%)
7		93% (92%-94%)
8		96% (95%-97%)
9		98% (97%-99%)

Updated from Zabor et al.[3]

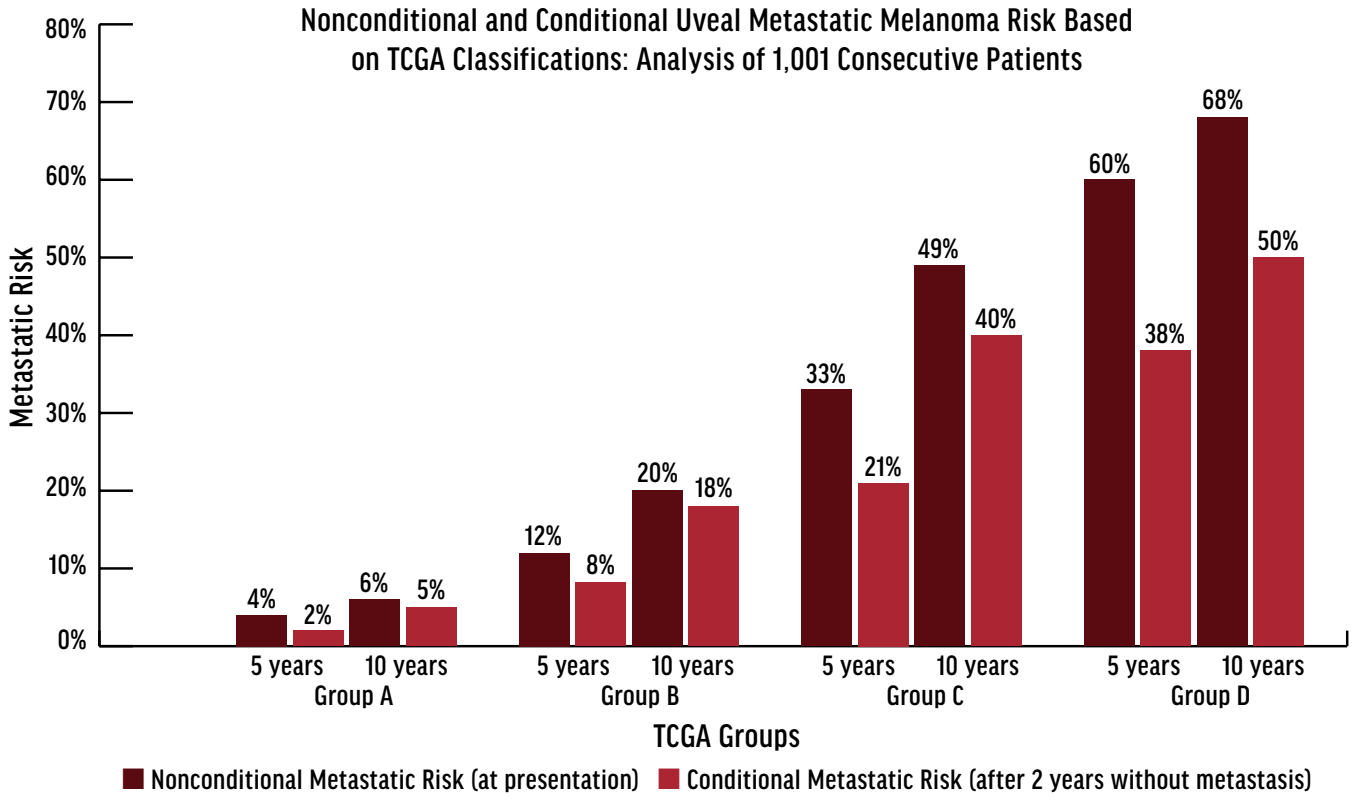

Figure 1. Comparison of cMR and ncMR of patients with uveal melanoma based on the TCGA classification system. The metastatic rate increases from Group A to Group D, but conditional survival improves when accounting for accrued years of metastasis-free survival. Adapted from Shields et al.[5]

based on genetic testing in 1,001 cases over a period of 22 years (Figure 1).[5] This analysis included TCGA Groups A (49%), B (14%), C (26%), and D (11%).[5] The nonconditional metastatic rate (ncMR) at presentation revealed 5- and 10-year metastatic rates of 4% and 6% (Group A), 12% and 20% (Group B), 33% and 49% (Group C), and 60% and 68% (Group D), respectively.[5] The conditional metastatic rate (cMR) after 2 years of metastasis-free survival yielded 5- and 10-year metastatic rates of 2% and 5% (Group A), 8% and 18% (Group B), 21% and 40% (Group C), and 38% and 50% (Group D), respectively.[5] These findings further suggest that longer survival without metastasis correlates with a reduction in metastatic risk. In addition, the researchers found that this decreased risk was most prominent in TCGA Group D.[5]

Relevance of Patient Age

To further explore the conditional survival estimates in patients with uveal melanoma, Shields et al studied a cohort of 8,091 patients with uveal melanoma over a maximum 51-year follow-up period, specifically evaluating conditional outcomes by age.[6] Patients with uveal melanoma who survived 3, 5, or 10 years without metastasis had improved probability of conditional survival compared with their initial prognosis.

At presentation, nonconditional cumulative incidence of metastasis (ncCIM) for 5-, 10-, 20-, 30-year survival was 15%, 23%, 32%, and 36%, respectively (Figure 2).[6] For patients who did not develop metastasis in the first 3 years, the conditional cumulative incidence of metastasis (cCIM) for 5-, 10-, 20-, and 30-year survival sdropped to 6%, 15%, 25%, and 30%, respectively.[6] The cCIM further improved in patients who remained metastasis-free at 5 years and showed even greater improvement when metastasis-free at 10 years. The cCIM fell to 13% and 18% for patients who reached 20- and 30-year survival, respectively.[6]

When accounting for patient age, the ncCIM revealed that the younger cohort (0-29 years of age) demonstrated significantly lower metastatic rates compared with the older cohort (80-99 years of age) with the 5-, 10-, 20-, and 30-year survival rates of 8%, 15%, and 19%, respectively, and 27% versus 21%, 29%, 29%, and 29%, respectively ($P < .001$).[6] Although the cCIM at 1 and 2 years of metastasis-free survival showed persistent superior younger cohort survival ($P < .001$ and $P = .001$, respectively), there was no further benefit for young patients at 3 years of metastasis-free survival.[6]

Conditional, dynamic prediction using Kaplan-Meier

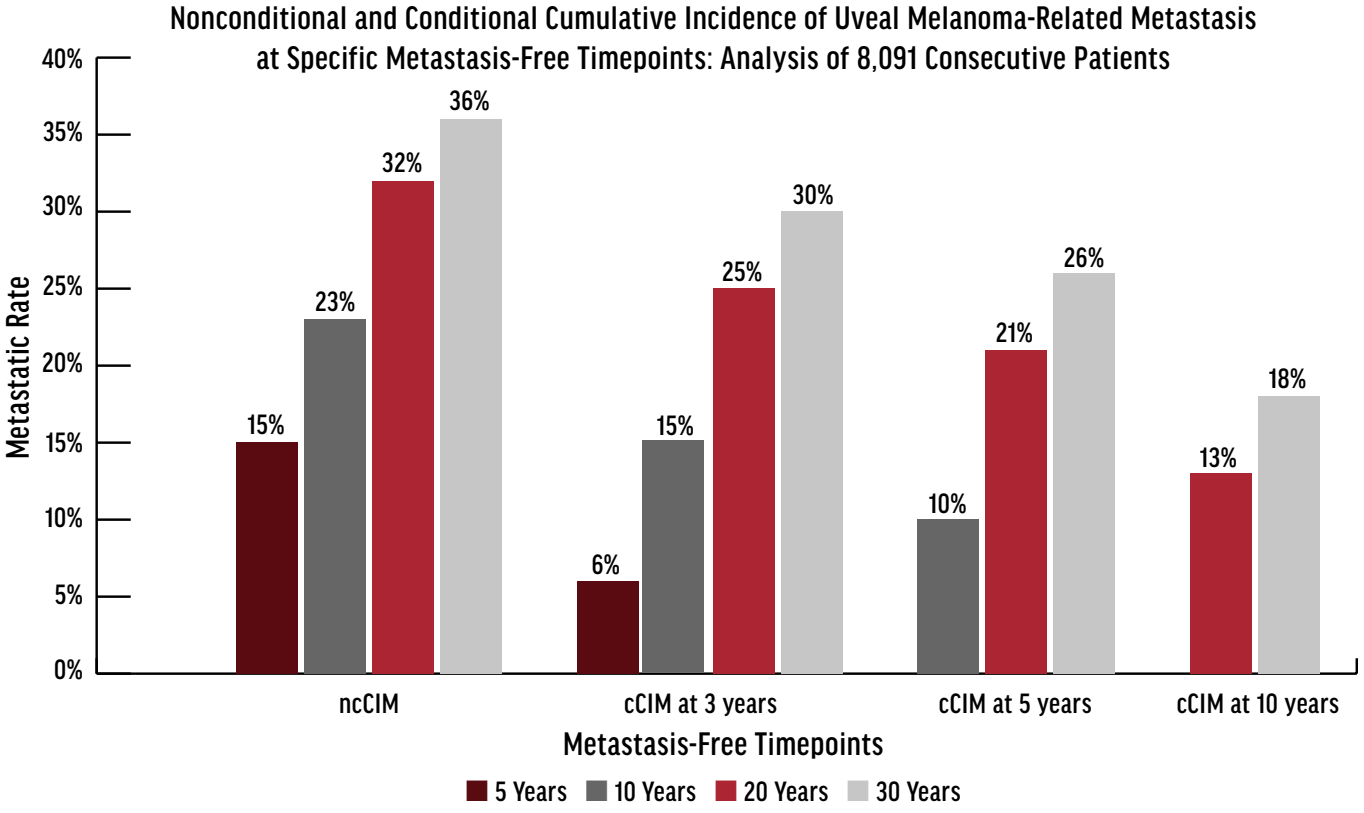

Figure 2. Comparsion of ncCIM versus cCIM at metastasis-free timepoints. The cCIM improves with accrued years of metastasis-free survival. Adapted from Shields et al.[6]

estimates can enhance our ability to counsel patients based on age and accrued years of metastasis-free survival.

PAINT A MORE ACCURATE PICTURE

Using conditional analysis, survival probability can provide clinicians with a more accurate tool to estimate individual patient prognosis, allowing for a more personalized understanding of their disease state. ■

Authors' note: Support provided in part by the Eye Tumor Research Foundation, Philadelphia, PA (CLS). The funders had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, or in the preparation, review and approval of the manuscript. Carol L. Shields, MD, has had full access to all the data in the study and takes responsibility for the integrity of the data.

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RISING STARS IN RETINA

Get to know outstanding retina fellows from the class of 2024.

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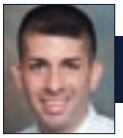

Jesse D. Sengillo, MD

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

I had an early interest in the field of retina, and I even applied to medical school with the intent of pursuing vitreoretinal surgery. My mother has a progressive retinal condition that caused her to become legally blind in her early 30s. Witnessing the profound effect the condition has on her provides me with constant motivation for finding the best ways to help patients and push the boundaries of our field.

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

I feel very fortunate to have mentors past and present who continue to provide selfless guidance during my career. They include Audina M. Berrocal, MD; Stephen H. Tsang, MD, PhD; Harry W. Flynn Jr, MD; Thomas A. Albini, MD; Jayanth Sridhar, MD; Bryon L. Lam, MD; Ninel Z. Gregori, MD; and Justin H. Townsend, MD. In addition, I must thank my program directors, Steven J. Gedde, MD, and Chris R. Alabiad, MD, and the chair, Eduardo C. Alfonso, MD. They, among many others, are very invested in their trainees, and I am grateful for their advice and support at every stage of my training.

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

Watching Dr. Berrocal perform gene therapy on one of her patients with Leber congenital amaurosis was particularly influential for me. I have been following the initial translational work and breakthroughs for inherited retinal disease since I was a child, hoping it would one day be applicable to my mom's condition. Having the opportunity to observe, in person, how research has advanced to a point of clinical application for patients with previously untreatable and blinding disease will always stay with me.

_RT:_ What are you hoping to accomplish once you are in practice?

I am very excited to join the faculty at the Bascom Palmer Eye Institute later this year as part of the new Mark J. Daily Inherited Retinal Diseases Research Center. I hope to bridge my passion for both ocular genetics research and vitreoretinal surgery to provide personalized, compassionate, and advanced care for patients with retinal pathology, especially inherited retinal diseases.

FIRST CAREER MILESTONE

Dr. Sengillo is joining the faculty at the Bascom Palmer Eye Institute Mark J. Daily Inherited Retinal Diseases Research Center.

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

The field of retina is extremely exciting because there is diverse pathology, innovative research, and the ability to perform surgeries that restore vision. With these opportunities and a quickly evolving field, it is extremely important to remember that the patient is the top priority and advocate for them. ■

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(Continued from page 50)

FIGURE 2

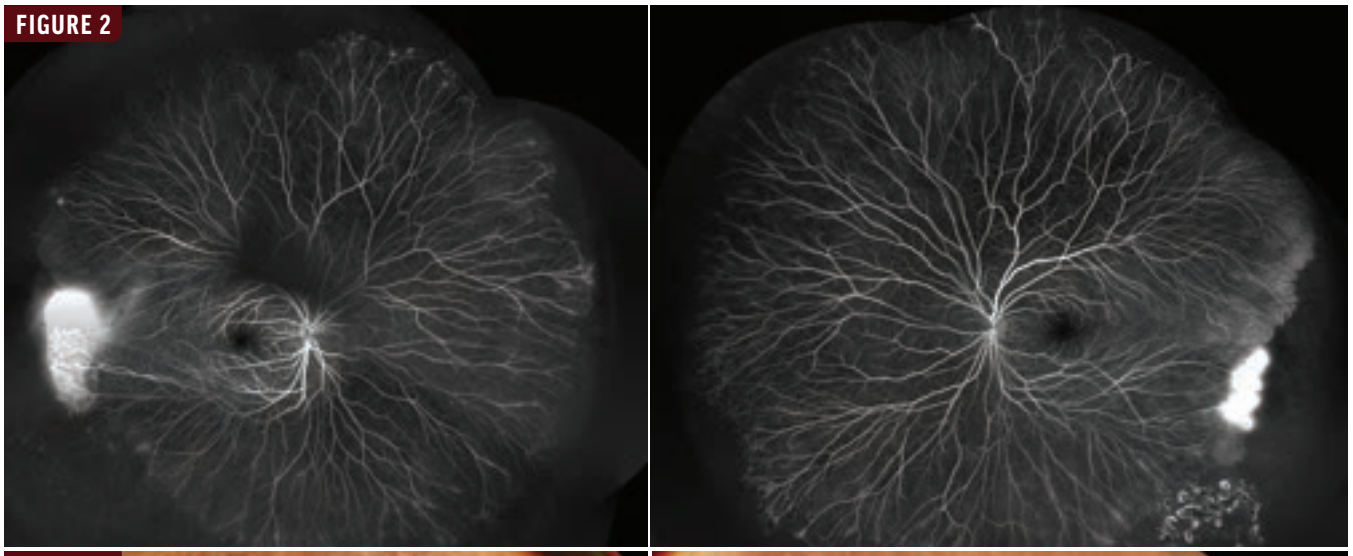
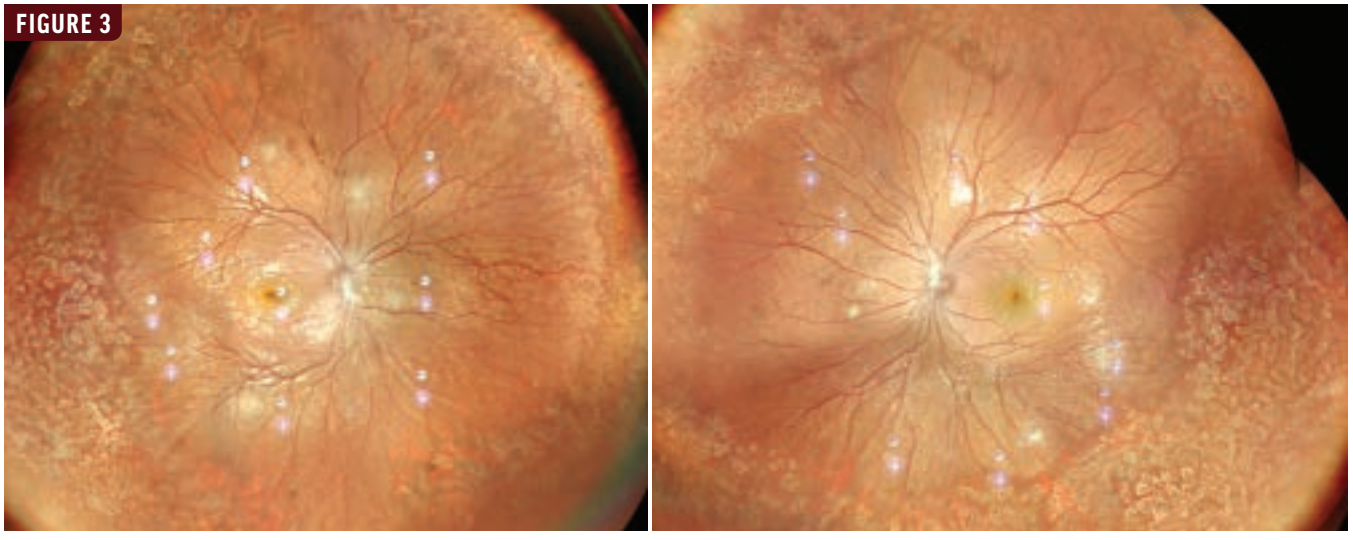


FIGURE 3



Stage 3: extramacular retinal detachment (RD)
Stage 4: macula-involving, subtotal RD
Stage 5: total RD

Stage 1 FEVR often goes undiagnosed due to the lack of symptoms. FEVR usually has a progressive course during childhood and may become stable after 20 years of age; however, late progression with vision-threatening complications, such as vitreous hemorrhage and RD, can occur at any age.

MANAGEMENT

Treatment protocols include observation, laser photocoagulation, and surgery (ie, vitrectomy or scleral buckling), depending on the disease stage. Long-term monitoring is required. Examination of the family members is also critical so that early intervention can be planned before complications develop. ■

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If you have images you would like to share, email Dr. Nagpal at drmanishnagpal@yahoo.com.

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

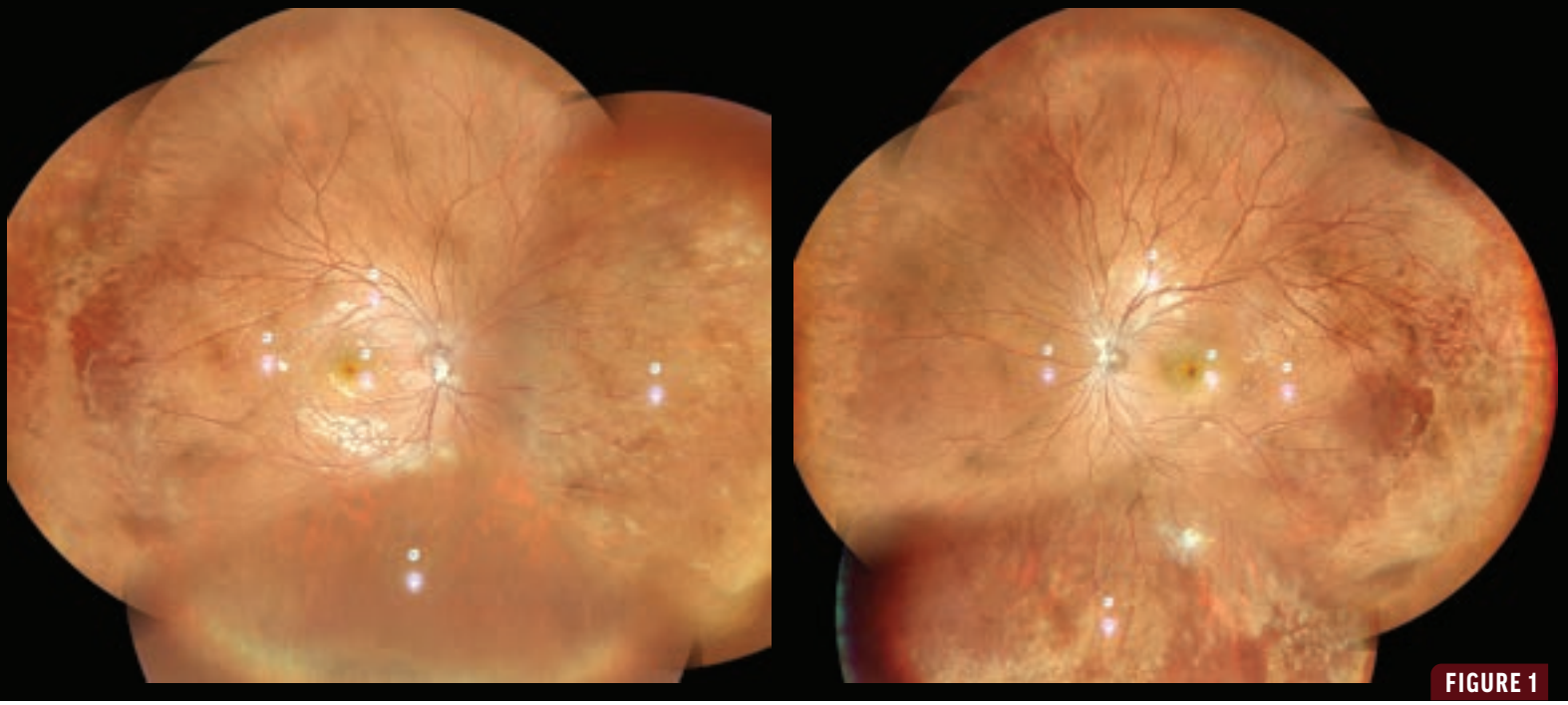

FIGURE 1

CATCHING FAMILIAL EXUDATIVE VITREORETINOPATHY EARLY

Know the first signs of this inherited retinal disease to initiate prompt treatment and monitoring.

BY VAIDEHI SATHAYE, MS; MANISH NAGPAL, MS, FRCS, FASRS; AND NAVNEET MEHROTRA, DNB, FRF

A 13-year-old boy was brought to our clinic for a routine visit. His birth history was normal, and there was no significant family history. On examination, his VA was 20/20 OU. His IOP was 20 mm Hg OD and 19 mm Hg OS. The anterior segment examination was within normal limits. Dilated fundus examination revealed avascular ischemic areas in the periphery of each eye, with a normal posterior pole (Figure 1).

Fluorescein angiography showed 360° capillary nonperfusion in the periphery with leakage secondary to neovascular proliferations in the temporal periphery of each eye (Figure 2).

A diagnosis of stage 1 familial exudative vitreoretinopathy (FEVR) was made, and the patient was treated with laser photocoagulation. At the 1-month follow-up, each eye showed a well-lasered retinal periphery (Figure 3). The patient will be evaluated again 4 to 6 months post-treatment.

STAGING

FEVR is a hereditary vitreoretinal disorder in which there is abnormal retinal angiogenesis, resulting in incomplete peripheral retinal vascularization and retinal ischemia. A clinical classification describes five stages of FEVR[1]:

Stage 1: avascular periphery or anomalous intraretinal vascularization

Stage 2: avascular retinal periphery with extraretinal vascularization

(Continued on page 49)

VABYSMO™
faricimab-svoa injection 6 mg

VABYSMO® (faricimab-svoa) injection, for intravitreal use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information

1 INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) inhibitor indicated for the treatment of patients with:

1.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

1.3 Macular Edema Following Retinal Vein Occlusion (RVO)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO *[see Adverse Reactions (6.1)]*. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept *[see Clinical Studies (14.1)]*.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

The incidence of reported ATEs in the RVO studies during the first 6 months was 1.1% (7 out of 641) in patients treated with VABYSMO compared with 1.4% (9 out of 635) in patients treated with aflibercept *[see Clinical Studies (14.3)]*.

5.4 Retinal Vasculitis and/or Retinal Vascular Occlusion

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of VABYSMO *[see Adverse Reactions (6.2)]*. Discontinue treatment with VABYSMO in patients who develop these events. Patients should be instructed to report any change in vision without delay.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*
- Endophthalmitis and retinal detachments *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*
- Retinal Vasculitis and/or Retinal Vascular Occlusion *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial 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.

The data described below reflect exposure to VABYSMO in 2,567 patients, which constituted the safety population in six Phase 3 studies *[see Clinical Studies (14.1, 14.2, 14.3)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO			Active Control (aflibercept)		
	AMD N=664	DME N=1,262	RVO N=641	AMD N=662	DME N=625	RVO N=635
Cataract	3%	15%	< 1%	2%	12%	1%
Conjunctival hemorrhage	7%	8%	3%	8%	7%	4%
Vitreous detachment	3%	5%	2%	3%	4%	2%
Vitreous floaters	3%	4%	2%	2%	3%	2%
Retinal pigment epithelial tear[a]	3%			1%		
Intraocular pressure increased	3%	4%	1%	2%	3%	3%
Eye pain	3%	3%	< 1%	3%	3%	< 1%
Intraocular inflammation[b]	2%	1%	1%	1%	1%	< 1%
Eye irritation	1%	< 1%	< 1%	< 1%	1%	< 1%
Lacrimation increased	1%	1%	0%	1%	< 1%	< 1%
Ocular discomfort	1%	1%	< 1%	< 1%	< 1%	< 1%

[a]AMD only
[b]Including iridocyclitis, iritis, uveitis, vitritis

Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, ocular hyperemia, blurred vision, sensation of foreign body, endophthalmitis, conjunctival hyperaemia, visual acuity reduced, visual acuity reduced transiently, vitreous hemorrhage, retinal tear and rhegmatogenous retinal detachment.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VABYSMO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: retinal vasculitis with or without retinal vascular occlusion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VABYSMO administration in pregnant women.

Administration of VABYSMO to pregnant monkeys throughout the period of organogenesis resulted in an increased incidence of abortions at intravenous (IV) doses 158 times the human exposure (based on C_{max}) of the maximum recommended human dose *[see Animal Data]*. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and 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 is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

An embryo fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 or 3 mg/kg. A non-dose dependent increase in pregnancy loss (abortions) was observed at both doses evaluated. Serum exposure (C_{max}) in pregnant monkeys at the low dose of 1 mg/kg was 158 times the human exposure at the maximum recommended intravitreal dose of 6 mg once every 4 weeks. A no observed adverse effect level (NOAEL) was not identified in this study.

8.2 Lactation

Risk Summary

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

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

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 following the last dose of VABYSMO.

Infertility

No studies on the effects of faricimab on human fertility have been conducted and it is not known whether faricimab can affect reproduction capacity. Based on the mechanism of action, treatment with VABYSMO may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

8.5 Geriatric Use

In the six clinical studies, approximately 58% (1,496/2,571) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following VABYSMO administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with VABYSMO and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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*Primary endpoint of non-inferiority vs aflibercept 2 mg in the mean change from baseline in BCVA was measured by the ETDRS letter score and tested using a margin of 4 letters. **nAMD:** VABYSMO met its primary endpoint of non-inferiority at year 1 (avg. of weeks 40, 44, and 48). Differences in LS means for VABYSMO were +0.7 letters (CI: [95%] -1.1, +2.5) in TENAYA; and 0.0 letters (CI: [95%] -1.7, +1.8) in LUCERNE. **DME:** VABYSMO met its primary endpoint of non-inferiority at year 1 (avg. of weeks 48, 52, and 56). Differences in LS means in YOSEMITE were +0.7 letters (CI: [97.5%] -1.1, +2.5) for VABYSMO Q4W–Q16W and -0.2 letters (CI: [97.5%] -2.0, +1.6) for VABYSMO Q8W. Differences in LS means in RHINE were +0.5 letters (CI: [97.5%] -1.1, +2.1) for VABYSMO Q4W–Q16W and +1.5 letters (CI: [97.5%] -0.1, +3.2) for VABYSMO Q8W. A non-inferiority margin was not available for year 2. **RVO:** VABYSMO met its primary endpoint of non-inferiority at week 24. Differences in LS means for VABYSMO were -0.6 letters (CI: [95%] -2.2, +1.1) in BALATON; and -0.4 letters (CI: [95%] -2.5, +1.6) in COMINO.[1]

†**nAMD:** 4 monthly loading doses followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform Q16W (weeks 28 and 44), Q12W (weeks 24, 36, and 48), Q8W (weeks 20, 28, 36, and 44), or Q4W (no added benefit) dosing. **DME:** at least 4 monthly loading doses followed by extensions ≤4 weeks or reductions ≤8 weeks based on OCT and visual acuity evaluations OR 6 monthly loading doses followed by Q8W. Q4W dosing may be needed (no added benefit). **RVO:** every month (4 weeks) for 6 months.[1]

INDICATIONS
VABYSMO (faricimab-svoa) is a vascular endothelial growth factor (VEGF) inhibitor and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME), and Macular Edema following Retinal Vein Occlusion (RVO).

IMPORTANT SAFETY INFORMATION

Contraindications
VABYSMO is contraindicated in patients with ocular or periocular infection, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

Warnings and Precautions
Endophthalmitis and Retinal Detachments
Intravitreal injections have been associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately.

Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept.

The incidence of reported ATEs in the RVO studies during the first 6 months was 1.1% (7 out of 641) in patients treated with VABYSMO compared with 1.4% (9 out of 635) in patients treated with aflibercept.

Retinal Vasculitis and/or Retinal Vascular Occlusion
Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of VABYSMO. Healthcare providers should discontinue treatment with VABYSMO in patients who develop these events. Patients should be instructed to report any change in vision without delay.

Adverse Reactions
The most common adverse reactions (≥5%) reported in patients receiving VABYSMO were cataract (15%) and conjunctival hemorrhage (8%).

Pregnancy, Lactation, Females and Males of Reproductive Potential
Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO. Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch.
You may also report side effects to Genentech at (888) 835-2555.

Please see additional Important Safety Information in the full VABYSMO Prescribing Information.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2023.

BCVA=best corrected visual acuity; CI=confidence interval; ETDRS=Early Treatment Diabetic Retinopathy Study; LS=least squares; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

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