Wills Eye Resident Series: An older woman presents with severe vision loss, *p. 64*

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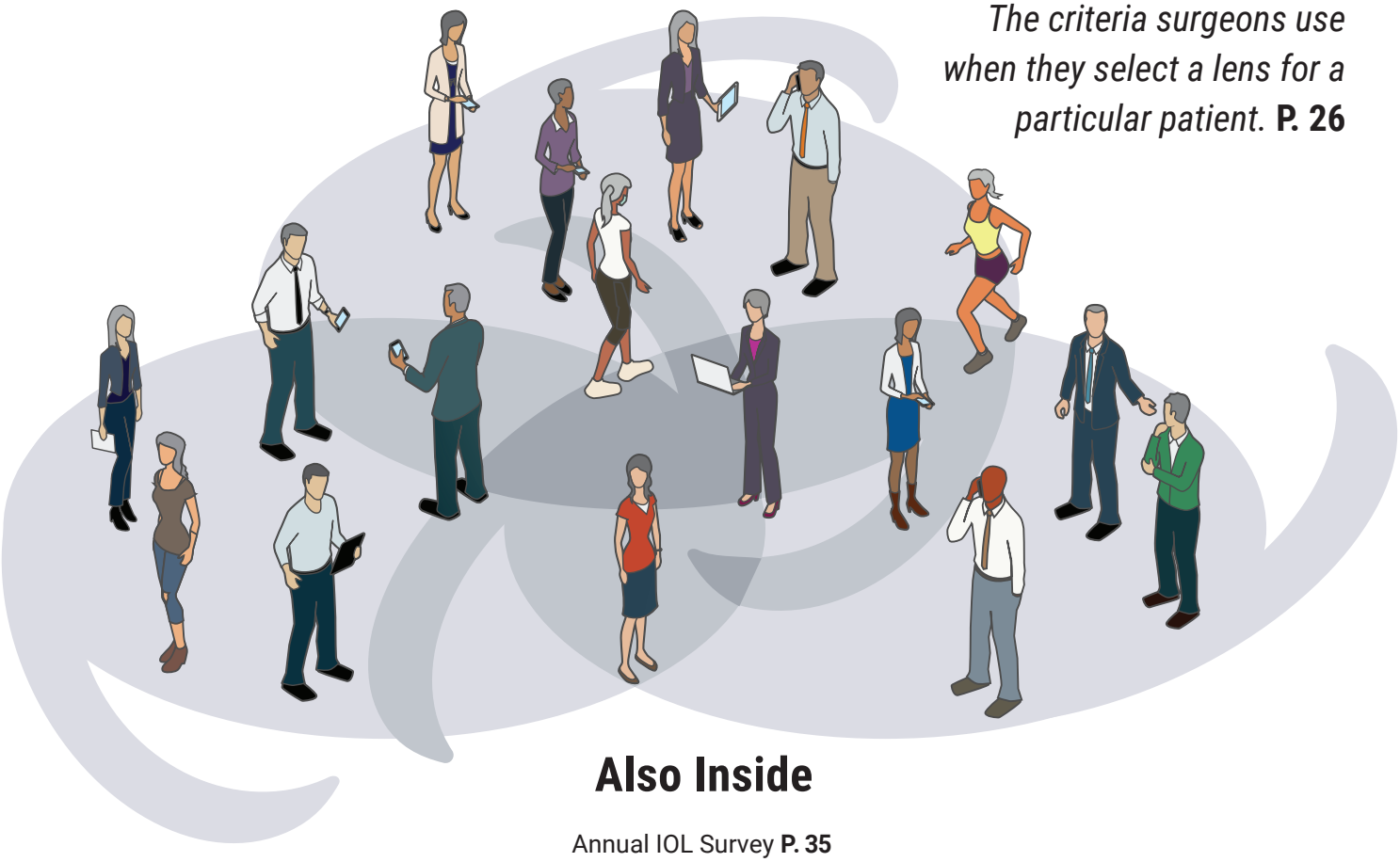
Matching the Right Patient With the Right Premium IOL

The criteria surgeons use when they select a lens for a particular patient. **P. 26**



Also Inside

VABYSMO™
faricimab-svoa injection 6 mg

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) and Diabetic Macular Edema (DME).

IMPORTANT SAFETY INFORMATION

Contraindications

VABYSMO is contraindicated in patients with ocular or periocular inflammation, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO.

Warnings and Precautions

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection.
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition.

Adverse Reactions

The most common adverse reaction (≥5%) reported in patients receiving VABYSMO was conjunctival hemorrhage (7%).

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 Brief Summary of VABYSMO full Prescribing Information on the following page.

*Dosing Information:

In nAMD, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for the first 4 doses, followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform whether to extend to: 1) Q16W (weeks 28 and 44); 2) Q12W (weeks 24, 36, and 48); or 3) Q8W (weeks 20, 28, 36, and 44).

In DME, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for ≥4 doses until CST is ≤325 µm (by OCT), followed by treat-and-extend dosing with 4-week interval extensions or 4- to 8-week interval reductions based on CST and visual acuity evaluations through week 52. Alternatively, VABYSMO can be administered IVT Q4W for the first 6 doses, followed by Q8W dosing over the next 28 weeks.

Although VABYSMO may be dosed as frequently as Q4W, additional efficacy was not demonstrated in most patients when VABYSMO was dosed Q4W vs Q8W. Some patients may need Q4W dosing after the first 4 doses. Patients should be assessed regularly and the dosing regimen reevaluated after the first year.

CST=central subfield thickness; IVT=intravitreal; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2022. **2.** Beovu® (brolucizumab) [package insert]. East Hanover, NJ: Novartis; 2020. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2021. **4.** LUCENTIS® (ranibizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **5.** SUSVIMO™ (ranibizumab injection) [package insert]. South San Francisco, CA: Genentech, Inc; 2022.

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THE WINDOW TO CHANGE

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)

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 during the first year was 2% (25 out of 1,262) in patients treated with VABYSMO compared with 2% (14 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

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)]*

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 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO		Active Control (aflibercept)	
	AMD N=664	DME N=1262	AMD N=622	DME N=625
Conjunctival hemorrhage	7%	7%	8%	6%
Vitreous floaters	3%	3%	2%	2%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	3%	2%	2%
Eye pain	3%	2%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	1%	< 1%	1%
Ocular discomfort	1%	1%	< 1%	< 1%
Vitreous hemorrhage	< 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, lacrimation increased, ocular hyperemia, blurred vision, eye irritation, sensation of foreign body, endophthalmitis, visual acuity reduced transiently, retinal tear and rhegmatogenous retinal detachment.

6.2 Immunogenicity

The immunogenicity of VABYSMO was evaluated in plasma samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VABYSMO in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VABYSMO with the incidence of antibodies to other products may be misleading.

There is a potential for an immune response in patients treated with VABYSMO. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is a potential for immunogenicity with VABYSMO.

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 four clinical studies, approximately 60% (1,149/1,929) 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.

VABYSMO™ [faricimab-svoa]
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M-US-00013249(v1.0) 2/22

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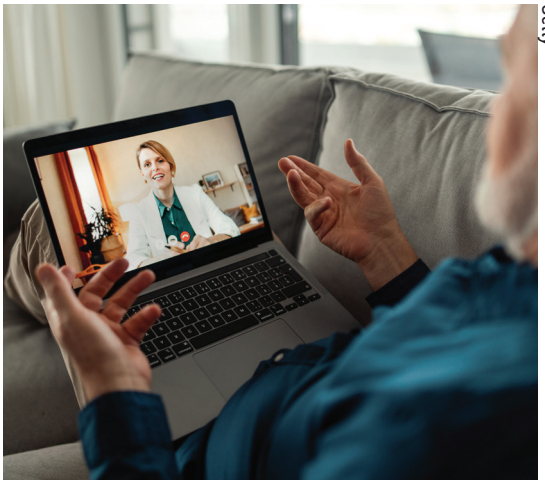
JANUARY 2023

Study: What the Pandemic Told Us about Tele-ophthalmology

Telehealth in eye care has historically followed the "store-and-forward" model, wherein retinal photography is combined with remote interpretation for screening of ophthalmic diseases, such as diabetic retinopathy and retinopathy of prematurity, but is otherwise less useful than in some other medical fields. Did the pandemic experience change that in any way, positive or otherwise? A recent study published in *JAMA Ophthalmology* compared telehealth trends between different medical specialties and ophthalmic subspecialties at a major academic institution over 18 months, beginning at the onset of the COVID-19 pandemic. In April 2020, a hybrid model of care delivery was implemented wherein asynchronous data could be collected to enhance telehealth consultation with clinicians.

The hybrid model of augmented telehealth in the study increased the depth of remote evaluation across several subspecialties. On the other hand, its highest users were subspecialties that had lower telehealth adoption and are known to be less amenable to virtual practice (e.g., cornea and glaucoma). Asynchronous testing data from this program changed management in 25.4 percent of encounters and expanded telehealth use to new indications, including the postoperative assessment of corneal transplantation.[1]

The study's authors say that the use of asynchronous testing may help telehealth be more feasible in subspecialties such as retina and glaucoma, the exams of which are traditionally difficult to perform remotely.



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"Physician participation in the hybrid telehealth model was voluntary so we tried not to draw absolute conclusions on its relative utility between subspecialties," the authors note in an e-mail comment to *Review*. "Nonetheless, combining asynchronous testing with telehealth enabled the evaluation of certain conditions which conventionally had not been cared for remotely, highlighting new opportunities that lie ahead. Our work suggests that the hybrid model will be useful for most if not all subspecialties, and we suspect the degree will be correlated with the quality and range of data acquired."

The asynchronous data in the hybrid model included visual acuity, intraocular pressure measurement, pachymetry, visual field testing, OCT (macula or optic nerve), retinal photography, specular microscopy and slit lamp photography. The overall quality improvement study evaluated retrospective, longitudinal, observational data from the first 18 months of the COVID-19 pandemic (January 1, 2020, through July 31, 2021) for 881,080 patients receiving care from outpatient primary care, cardiology, neurology, gastroenterology, surgery, neurosurgery, urology, orthopedic surgery, otolaryngology, obstetrics/gynecology and ophthalmology.

The volume of in-person outpatient visits dropped by 83.3 percent (39,488 of 47,390) across the evaluated specialties at the onset of shelter-in-place orders for the COVID-19 pandemic, and the initial use of telehealth increased for these specialties before stabilizing over the 18-month study period. The highest use was found in gastroenterology, urology, neurosurgery and neurology, and the lowest use was in ophthalmology.

(Continued on p. 8)

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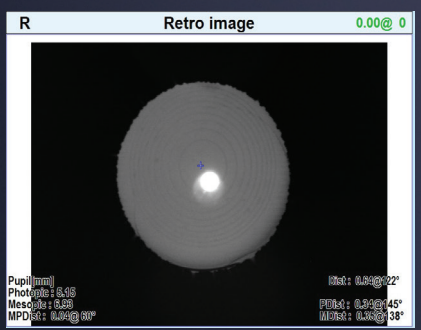

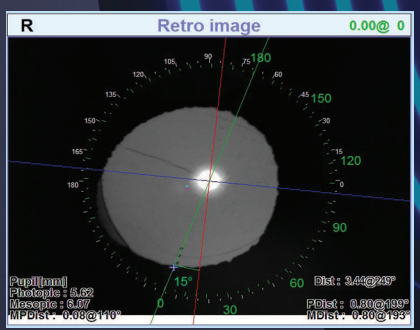

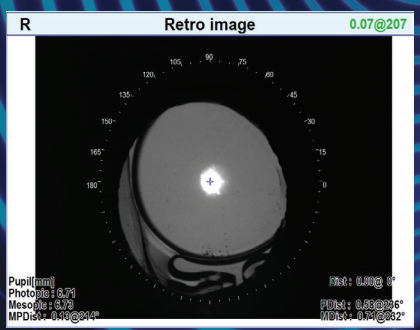

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PUBLISHER
MICHAEL HOSTER
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SENIOR MANAGER, STRATEGIC ACCOUNTS
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GA lesions can lead to visual impairment even before they reach the fovea[1,5,6]

See the effect of GA progression on your patients

*Data sourced from the Age-related Eye Disease Study (AREDS) Report #26—a long-term, multicenter, prospective study examining progression of GA area in a cohort of 3640 patients with signs of early and more advanced forms of AMD.

†A retrospective cohort analysis (N=1901) of a multicenter electronic medical record database examining disease burden and progression in patients in the United Kingdom with bilateral GA secondary to AMD.

BCVA=best-corrected visual acuity.

References: 1. Boyer DS et al. *Retina*. 2017;37:819-835. 2. Lindblad AS et al, and AREDS Research Group. *Arch Ophthalmol*. 2009;127(9):1168-1174. 3. Holz FG et al. *Ophthalmology*. 2014;121(5):1079-1091. 4. Sunness JS et al. *Ophthalmology*. 2007;114(2):271-277. 5. Kimel M et al. Invest *Ophthalmol Vis Sci*. 2016;57(14):6298-6304. 6. Sadda SR et al. *Retina*. 2016;36(10):1806-1822. 7. Singh RP et al. *Am J Ophthalmic Clin Trials*. 2019;(1):1-6. doi:10.25259/ajoct-9-2018. 8. Sivaprasad S et al. *Ophthalmol Ther*. 2019;8(1):115-124. 9. Patel PJ et al. *Clin Ophthalmol*. 2020;14:15-28. 10. Chakravarthy U et al. *Ophthalmology*. 2018;125:842-849.

Apellis

(Continued from p. 4)

Telehealth Use

Asynchronous testing was combined with 126 teleophthalmology encounters, resulting in change of clinical management for 32 patients (25.4 percent) and no change for 91 (72.2 percent). In ophthalmology, telehealth use peaked at 31 percent encounters early in the pandemic and returned to mostly in-person visits as COVID-19 restrictions were lessened. After the stay-at-home orders were lifted, ophthalmic use of telemedicine (1.1 percent) returned almost entirely to pre-pandemic levels, while other specialties continued to provide a considerable percentage of visits remotely (14.9 percent to 65.9 percent).

"Clinical decision making in ophthalmology relies heavily on examination and testing, which are typically acquired in-person and pose intrinsic barriers for telehealth," the authors state. "An important takeaway from our study was that asynchronous testing did make telehealth evaluation feasible in many cases, and one approach for overcoming these barriers."

Consistently, oculoplastics and pediatric ophthalmology, which often rely on external examination of the eye, had the greatest telehealth use during the COVID-19 shelter-in-place orders and, interestingly, maintained some level of telehealth even after the orders were lifted. However, these two specialities didn't use the asynchronous model, which suggested a relative reliance on external video examination. In contrast, the retina, glaucoma and cornea subspecialties, which rely more heavily on microscopic examinations and specialized tools to evaluate ocular health and anatomy, didn't employ telehealth services as often.

> **In ophthalmology, telehealth use peaked at 31 percent of encounters early in the pandemic and returned to mostly in-person visits as COVID-19 restrictions were lessened.**

"Telehealth use by ophthalmology was modest compared with other specialties, and patient care returned almost entirely to in-person settings by October 2020," the researchers noted in their paper.[1]

An interesting finding in the study is that separating testing from clinical examination could potentially help with clinic workflow.

"Telehealth has the potential to improve access to care as well as workflow efficiency," the authors say. "Clinic visits are often prolonged due to the need of specialized testing. Separating testing from the clinical visit creates opportunities to streamline workflow and wait times. Additionally, remote testing can be used to reach remote areas and expand the reach of ophthalmic care."

A commentary by Wilmer Eye Institute retina specialist David Glasser, also published in *JAMA Ophthalmology*, emphasized that the most important reason for the lag in ophthalmology's adoption of telehealth during the COVID-19 public health emergency perhaps lay in the visual nature of its practitioners' work. "Literally seeing the pathology is integral to our evaluation and management decisions to a greater degree than in most other specialties," writes Dr. Glasser. "The techniques and devices used to facilitate visualization are not easily transferable to a remote visit."[2]

Once clinicians developed protocols to reduce the risk of person-to-person spread, the author noted that hybrid systems gave way to the greater efficiency of same-day in-person testing and visits.[2]

"There are potential technological solutions to these limitations, offering the promise of access to care to remote and disadvantaged populations but only if the industry can realize a return on investment in developing new technology and healthcare professionals can use the resulting devices without incurring financial penalties," Dr. Glasser states.[2]

Though the study's findings are no doubt interesting, the authors acknowledge that it has some limitations. "A limitation of our study is that it was not designed to evaluate the long-term potential of teleophthalmology," they say. "Asynchronous testing was performed in the

(Continued on p. 16)

INDUSTRY NEWS

Cord Files for Premarket Approval for New Intraocular Lens

Cord, a privately held ophthalmic medical device company, recently announced that it's submitted a Premarket Approval application to the FDA for its Model SC9 Intraocular Lens.

The SC9 lens was designed to provide a monofocal spherical optic but has a rigid structure to "consistently locate the optic in a position intended to provide intermediate vision that is superior to that of a standard monofocal IOL," Cord says.

Oxurion to Continue KALAHARI Phase IIb Study in DME

Oxurion announced an Independent Data Monitoring Committee (IDMC) recommended continuation of the company's KALAHARI Phase II, Part B clinical trial evaluating Oxurion's investigational treatment for diabetic macular edema.

Ocuphire Pharma Submits Nyxol NDA to FDA

Ocuphire Pharma recently announced the submission of a New Drug Application to the FDA for phentolamine ophthalmic solution 0.75% (Nyxol) for the reversal of pharmacologically-induced mydriasis.

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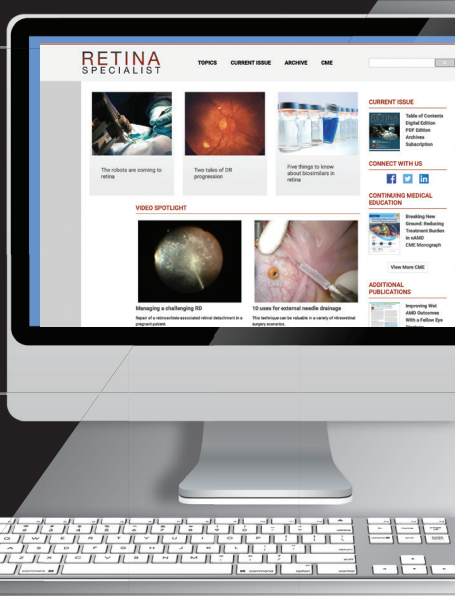

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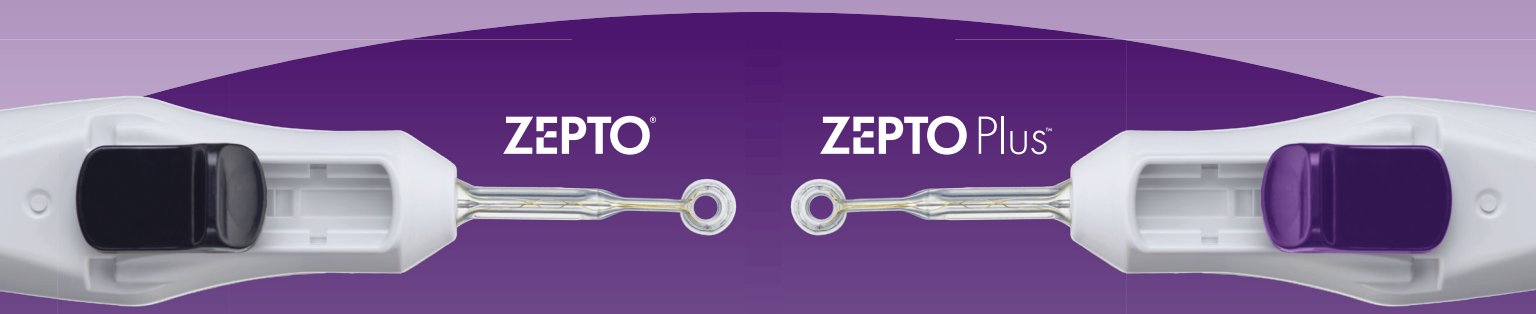

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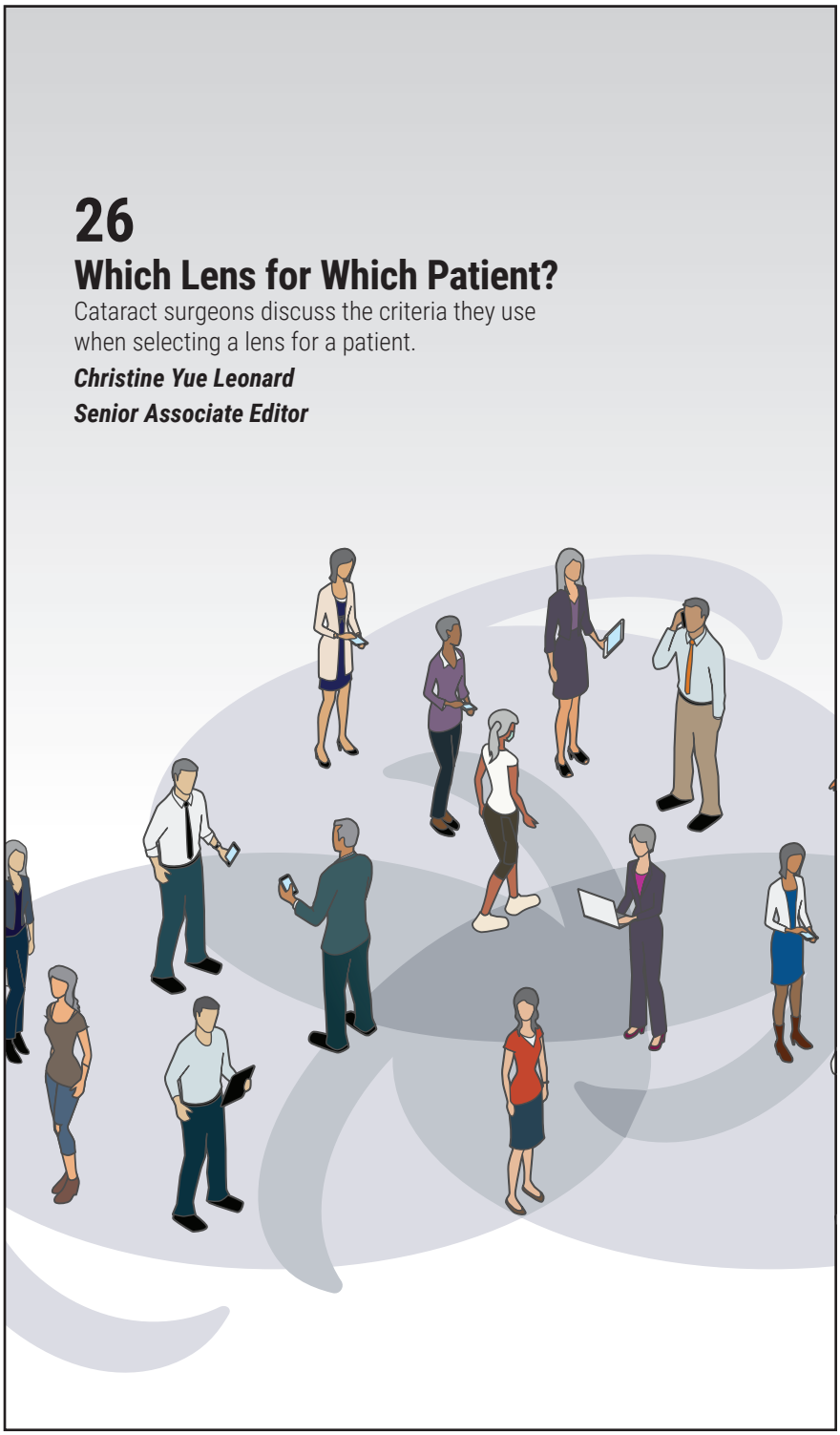

DEPARTMENTS

January 2023

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We're willing to bet most eye care professionals don't realize just how prevalent *Demodex* blepharitis is.[1]

In fact, ~**25 million eye care** patients in the US may have *Demodex* blepharitis (DB).[2]

DON'T BELIEVE US?
LEARN HOW DB CAN FLY UNDER THE RADAR AT

LOOK *at the* LIDS.COM

@LookAtTheLids | | | tarsus

References: 1. Data on file, Tarsus Pharmaceuticals, Inc. June 2022. **2.** O'Dell L et al. *Clin Ophthalmol.* 2022;16:2979-2987.

US--2200006 12/22

REVIEW of OPHTHALMOLOGY
EDITORIAL STAFF

Editor in Chief
Walter Bethke
(610) 492-1024
wbethke@jobson.com

Senior Editor
Christopher Kent
(212) 274-7031
ckent@jobson.com

Senior Editor
Liz Hunter
(610) 492-1025
ehunter@jobson.com

Senior Associate Editor
Christine Leonard
(610) 492-1008
cleonard@jobson.com

Associate Editor
Leanne Spiegle
(610) 492-1026
lspiegle@jobson.com

Chief Medical Editor
Mark H. Blecher, MD

Senior Art Director
Jared Araujo
(610) 492-1032
jaraujo@jobson.com

Graphic Designer
Lynne O'Connor
(267) 566-6007
lyoconnor@jobson.com

Business Offices
19 Campus Boulevard, Suite 101
Newtown Square, PA 19073
(610) 492-1000
Fax: (610) 492-1039

Subscription inquiries:
United States – (877) 529-1746
Outside U.S. – (845) 267-3065
E-mail:
revophthalmology@cambeywest.com
Website: www.reviewofophthalmology.com

WALTER C. BETHKE, EDITOR IN CHIEF
EDITOR'S PAGE

Sustained Delivery

In this month's feature on sustained delivery of glaucoma drugs (p. 43), Senior Editor Chris Kent speaks to experts on what some feel could be the holy grail of medically treating glaucoma: With sustained-release of a drug, the patient gets solid, steady efficacy over an extended period of time, while eliminating many possible negatives of treating via traditional delivery systems.

As physicians and researchers continue to hone their approach to this reliable, sustained delivery, it struck me that we at *Review* were lucky to have had a model of perfect "sustained delivery" right here at our publication: Chris Kent, who retired last month after 20 years on *Review of Ophthalmology*. This article—ironically on sustained delivery—was his last. Chris embodied the ideal of sustained delivery: Providing high-quality results, day in and day out—with barely any outside intervention—for an incredible length of time. Among his key attributes:

Ease of implantation: After placement at *Review of Ophthalmology*, in addition to already being a skilled writer in general, Chris already had several years of ophthalmology writing and editing experience under his belt. He was able to hit the ground running.

Safety: Chris Kent has never injured anyone—that I know of—and the only adverse reaction he's ever had was with Brussels sprouts. Otherwise, he gets along with everyone he meets: He's happy to converse with you about medicine, music, astronomy, Star Trek, literature, music, your family or music. Whatever topic comes up, he's probably got an interesting angle or insight on it (especially music).

In the magazine realm, if "safety" is blowing a deadline or putting a foot wrong in an article, then he's safe as houses.

Efficacy: This is the topper. When it comes to the quality of his articles, if Chris were actually a drug, he'd be designated "best-in-class." His work was always meticulously researched, and considered the topic from every conceivable angle.

And it's not only the depth of his work that stands out, but the breadth, as well. In his 20-year career at *Review*, the 700+ articles he's written have explored topics such as glaucoma diagnosis and treatment (his personal subspecialty), cataract/IOL surgery, refractive surgery of every flavor, private equity, practice management, MIPS and MACRA, retina, cornea, physician retirement strategies—the list goes on. If it's a topic that affects an ophthalmologist or his practice, chances are, Chris has covered it. And, when you finished any of his works, it was so comprehensive you felt like you could cut the article out and carry it with you as a "how-to" guide.

But those days of battling in the trenches to get the latest results and best quotes are behind him now. He can look forward to making his music (he's an accomplished singer, guitarist and songwriter with several albums to his name) and traveling the country with his charming wife Lynn.

Though we're sad to see Chris go, we're happy for him as he starts this exciting new chapter of his life.

We wish you nothing but the best, old friend!

— Walter Bethke
Editor in Chief

Alcon Vision Suite

Complete. Connected. Working as one.

SMARTCataract

Your practice working smarter

ARGOS®
The ARGOS® Biometer is your entry point to high-resolution image guidance and a smarter, connected practice.

Work more efficiently.[1-5] Prepare from anywhere. Get next-level accuracy.*

IMPORTANT PRODUCT INFORMATION
ARGOS® Optical Biometer

Caution: Federal (USA) law restricts this device to the sale by or on the order of a physician.

Indications: ARGOS® is a non-invasive, non-contact biometer based on swept-source optical coherence tomography (SS-OCT). The device is intended to acquire ocular measurements as well as perform calculations to determine the appropriate intraocular lens (IOL) power and type for implantation during intraocular lens placement.

Intended Use: The Reference Image functionality is intended for use as a preoperative and postoperative image capture tool. It is intended for use by ophthalmologists, physicians, and other eye-care professionals and may only be used under the supervision of a physician.

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- Factors that influence the measurement of patient's eyes are listed in the User Manual (Table 1): pseudophakic eye, wearing contact lenses, fixation problem, cornea opacity, non-intact cornea, refractive surgery, blood in the vitreous humor, retinal detachment, keratoconus, asteroid hyalosis, ambient light in the room, and deformation of the corneal shape. Please consider the guidance provided in Table 1 when you encounter these factors.
- Optical Radiation - This device is equipped with a Class 1 laser light source.

ATTENTION: Refer to the ARGOS® User Manual for a complete description of proper use and maintenance, optical and technical specifications, as well as a complete list of warnings and precautions.

*Enabled with integrated Image Guidance by Alcon

References
1. Alcon Data on File, 2020. **2.** Blaylock JF, Hall B. Astigmatic results of a diffractive trifocal toric IOL following intraoperative aberrometry guidance. *Clin Ophthalmol*. 2020;14:4373-4378. doi:10.2147/OPTH.S285711 **3.** Cionni RJ, Dimalanta R, Breen M, Hamilton C. A large retrospective database analysis comparing outcomes of intraoperative aberrometry with conventional preoperative planning. *J Cataract Refract Surg*. 2018;44(10):1230-1235. doi:10.1016/j.jcrs.2018.07.016 **4.** Van Vliet EJ, Bredenhoff E, Sermeus W, Kop LM, Sol JCA, Harten WH. Exploring the relation between process design and efficiency in high-volume cataract pathways from a lean thinking perspective. *Int J Qual Health Care*. 2011;23(1):83-93. doi:10.1093/intqhc/mzq071 **5.** Håkansson I, Lundström M, Stenevi U, Ehinger B. Data reliability and structure in the Swedish National Cataract Register. *Acta Ophthalmol Scand*. 2001;79(5):518-523. doi:10.1034/j.1600-0420.2001.790519.x

(Continued from p. 8)

Telehealth Use

same buildings as in-person appointments, and it was more convenient for our department to return to in-person visits once COVID-19 restrictions were lifted. Use of remote testing sites will be a better approach for assessing whether the hybrid model is feasible long-term."

The authors say that they plan to continue to study the topic of telehealth in ophthalmology. "We hope to study the prospective sustainability of this new model of care from a financial and logistical standpoint," the say. "It will also be critical to further study and learn about the blind-spots associated with telemedicine, since we certainly don't want to cause harm by missing disease."

1. Mosenia A, Li P, Seefeldt R, et al. Longitudinal use of telehealth during the COVID-19 pandemic and utility of asynchronous testing for subspecialty-level ophthalmic care. JAMA Ophthalmol. December 1, 2022. [Epub ahead of print].
2. Glasser DB. Is there a future for telehealth in ophthalmology? JAMA Ophthalmol. December 1, 2022. [Epub ahead of print].

First Dose of COVID Vaccine May Cause Uveitis to Flare

A recent study demonstrated an increased risk of uveitis flare following COVID vaccination. This risk was highest among those with previous recurrence, chronic uveitis and a shorter period of quiescence.

The retrospective study identified participants from the Inflammatory Eye Disease Registry at Auckland District Health Board who were diagnosed with uveitis between January 1, 2010, and December 31, 2020. The date of COVID vaccination was determined from the patient's clinical record, and the rate of flare was calculated for three months prior to vaccination and for three months after each vaccination. Uveitis flare was defined as the presence of new or increased uveitis activity that required a change in treatment.

A total of 4,184 eyes of 3,008 patients were included, with a total of 8,474 vaccinations given during the study period. The median age was 54.8 years, and 1,474 (49 percent) of the participants were female.

Noninfectious etiology was most common, occurring in 2,296 patients (76.3 percent), with infectious etiology in 712 (23.7 percent). The rate of uveitis flare was 12.3 per 1,000 patient months at baseline, 20.7 after the first dose, 15 after the second, 12.8 after the third and 23.9 after the fourth. The median period of quiescence prior to flare was 3.9 years. An increase in uveitis flare was seen both in infectious uveitis (13.1 at baseline compared with 20.2 after first dose) and noninfectious uveitis (12.4 at baseline compared with 20.9 after first dose).

Risk factors for uveitis flare were identified to be recurrent uveitis, chronic uveitis, a shorter period of quiescence and the first dose of the COVID-19 vaccine. Median time to uveitis flare was 0.53 months following the first vaccination, 1.74 months following the second and 1.35 months following the third."

Jordan CA, Townend S, Allen N, et al. Navigating COVID-19 vaccination and uveitis: identifying the rates and risk of recurrent uveitis following COVID vaccination. Ophthalmology. December 16, 2022. [Epub ahead of print].

New Research Breaks Down Central Serous Chorioetinopathy

Previously, central serous chorioretinopathy has been classified as either acute or chronic depending on disease duration, but thresholds vary from study to study. A recent alternative classification system categorizes the disease as either simple or complex based on whether the retinal pigment epithelium alteration region is greater than two disc areas. A third atypical type of CSC was classified to include bullous variant, RPE tear and association with other retinal diseases. A team of researchers used the revised system in a new study to investigate the clinical and genetic characteristics of simple vs. complex CSC.

The study evaluated 319 patients with idiopathic CSC. Disease type was determined based on the presence or absence of retinal pigment alterations greater than two disc areas in either eye. Among the cohort, 53 patients (16.6 percent) had the complex type, which was seen exclusively in males (100 percent), and most of the patients with the simple type were also male (79 percent).

The team also found that compared with patients with the simple type, those with the complex type had a significantly higher proportion of bilateral involvement and descending tract(s). Complex CSC patients also had a thicker choroid (425 µm vs. 382 µm) and thinner central retina (274 µm vs. 337 µm) compared with simple CSC patients.

The study also genotyped CFH variants rs800292 and rs1329428. The researchers reported that the "risk allele frequencies of both variants were significantly higher in the complex vs. simple type."

The researchers say, "The risk allele of the CFH gene is associated with an RPE alteration greater than a two-disc area, including patchy atrophy and descending tract(s). Although this study was cross-sectional, genotyping these variants might be useful for predicting RPE atrophy development and enlargement." ◀

Yoneyama S, Fukui A, Sakurada Y, et al. Distinct characteristics of simple versus complex central serous chorioretinopathy. Retina. December 7, 2022. [Epub ahead of print].

PRODUCT NEWS

New items on the market to improve clinical care and strengthen your practice.

GLAUCOMA THERAPY

FDA Approves Preservative-free Latanoprost Option

The FDA recently approved the first preservative-free formulation of latanoprost for intraocular pressure reduction in patients with open-angle glaucoma or ocular hypertension. The new drug, Iyuzeh (Thea Pharma), is bottled without the use of benzalkonium (BAK) and other preservatives used in topical ocular preparations, Thea says. According to the company, this will help avoid patients experiencing the moderate to severe signs and symptoms of ocular surface disease associated with such preservatives.

Thea Pharma adds that this product solves a unique challenge of solubilizing and stabilizing latanoprost in that Iyuzeh doesn't need to be manufactured, distributed or stored at refrigerated temperatures.

In multiple trials across the United States and Europe, Iyuzeh demonstrated consistent IOP-lowering effects and tolerability, Thea says. It lowered IOP by 3 to 8 mmHg in patients with OAG or OHT with a mean baseline IOP of 19 to 24 mmHg, compared to the BAK-preserved Xalatan's 4 to 8 mmHg.

The recommended dose of Iyuzeh is one drop in the affected eye(s) once daily in the evening. The company says reduction of the IOP begins three to four hours after administration, with the maximum effect achieved after eight to 12 hours, lasting at least 24 hours. The most frequently reported ocular adverse events in the clinical trials included conjunctival hyperemia and eye irritation.

For more information about IYUZEH, visit theapharmainc.com.

LOW VISION

Transforming Light

For your low-vision patients who may need some more light to read or accomplish near tasks, Eschenbach Optik of America has released a new combination product, the Magno Travel Lamp.

The new lamp is a compact, multi-use lighting tool, the company says. The Magno Travel Lamp doubles as both a desk lamp and a flashlight. The LED lamp weighs less than a pound, and features a rechargeable battery that lasts eight hours for the lamp function and five hours for the flashlight, Eschenbach says.

For the desk-lamp function, the lamp head folds out and extends to a height of 18 inches. Users can choose from three color temperature settings: warm yellow 3,200K, neutral white 4,200K and cool white 6,000K, all

of which can be dimmed from 100 percent to 10 percent with the touch of a button. Folding the lamp head in transforms it into a handheld flashlight that measures 10.5 inches.

More information about the Magno Travel Lamp can be found at eschenbach.com.

AMBLYOPIA

CureSight Rolls Out

In 2022, NovaSight announced the FDA clearance of CureSight, its new eye-tracking-based amblyopia treatment device. Designed for at-home use, CureSight helps amblyopic eyes learn to work together while streaming a video of the child's choice through the red-blue treatment glasses. The device officially began rolling out to the company's Physician's Early Adopter Program at the end of 2022. The next phase will occur during the first half of 2023, launching to several hundred physicians who signed up for CureSight's referral program, says the company. Physicians should note there are three unique CPT codes for CureSight and NovaSight is aiming to reach coverage from the top five U.S. insurance payers in 2023.

For more information, visit nova-sight.com. ◀

NovaSight says its CureSight device's red-blue treatment glasses help treat amblyopic children's eyes as they stream videos.

Association Between Myopia and POAG/IOP

Researchers used Mendelian randomization (MR) analysis to determine genetic causal associations between myopia, glaucoma and glaucoma-related traits to overcome the effects of external confounders.

The study doctors analyzed bi-directional genetic associations between myopia or refractive spherical equivalent (RSE), POAG and POAG-endophenotypes. They analyzed data from a genetic bank (n=216,257 to 542,934), and used multiple Mendelian randomization models and multivariate genomic structural modeling to identify significant mediators for the relationship between myopia and POAG.

Here are some of the findings:

• Researchers found consistent bi-directional genetic associations between myopia and POAG, and between myopia and intraocular pressure using multiple MR models at Bonferroni-corrected levels of significance.

• IOP had the most significant mediation effect on RSE and POAG (Sobel test: 0.13; CI, 0.09 to 0.17; $p=1.37\times10^{-8}$).

Researchers found a strong bi-directional genetic causal link between myopia and POAG, which was mainly mediated by IOP. The findings suggested IOP-lowering treatment for glaucoma may be beneficial in myopic eyes, despite the challenges of establishing a clear clinical diagnosis, they added.

Ophthalmology 2022; Dec 6. [Epub ahead of print]
Chong RS, Li H, Cheong AJ, et al.

Changes after Aflibercept Treat and Extend

Investigators examined the morphological changes in macular neovascularization secondary to age-related macular degeneration after two years of aflibercept treatment under a treat-and-extend regimen.

This retrospective study analyzed the medical records for 26 eyes of 25 patients diagnosed with treatment-naïve neovascular AMD and treated with aflibercept under a T&E regimen for two years. The areas of the MNV and vascular structures were assessed using swept-source optical coherence tomography angiography at baseline and after two years of treatment.

Here are some of the findings:

• The mean MNV area increased significantly from 0.65 ±0.42 mm^2 at baseline to 0.78 ±0.45 mm^2 at two years.

• At two years, the mean change in the MNV area from baseline was 22 percent (interquartile range: 4 to 60 percent).

• The baseline MNV area was negatively correlated with the change ratio of the MNV areas at two years and baseline (R=-0.68; $p<0.001$).

• Nine of 26 eyes (34.6 percent) showed newly formed mature vessels, and seven eyes (26.9 percent) showed prominently developing preexisting mature vessels.

Investigators determined MNV expanded and showed vascular maturation under aflibercept treatment with a T&E regimen. They added, the smaller the MNV at baseline, the greater was its expansion in two years.

Retina 2022; Nov 17. [Epub ahead of print].
Nakano Y, Takeuchi J, Horiguchi E, et al.

Detecting Optic Disc Drusen

Researchers evaluated the most accurate diagnostic imaging modality to detect optic disc drusen (ODD) between B-scan ultrasonography (U/S), fundus photography, fundus autofluorescence (FAF) and enhanced depth imaging optical coherence tomography (EDI-OCT).

The comparative diagnostic analysis included 205 eyes of 105 patients with suspected ODD. Of these, 108 had ODD. All eyes received a full in-person ophthalmic exam with 3D view of the optic nerve and all four imaging modalities.

Here are some of the findings:

• EDI-OCT had the highest sensitivity (95 percent) and accuracy (97 percent) to detect ODD, compared to:

— FAF (sensitivity, 84 percent; accuracy, 92 percent);

— U/S (sensitivity, 74 percent; accuracy, 86 percent); and

— fundus photography (sensitivity, 38 percent; accuracy, 66 percent).

• All image modalities had high specificity (>97 percent) and precision (>93 percent).

• enhanced depth-imaging OCT had the highest examiner confidence (96 percent) compared to the others (88 percent).

Researchers determined that, among the four imaging modalities, enhanced depth-imaging OCT had the highest diagnostic utility for the detection of optic disc drusen and suggested it should be considered the preferred initial diagnostic modality.

Am J Ophthalmol 2022; Dec 11. [Epub ahead of print]
Youn S, MFE B, Armstrong JJ, et al.

Don't Let the Sun Go Down on Me

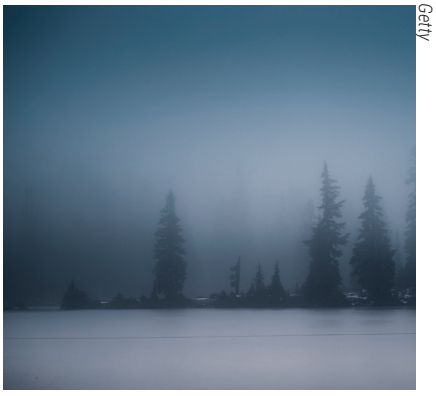
Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

By the time you're reading this column, the worst will be over. The days will be starting to get longer. Maybe not perceptibly, but that depends on where you are. Latitude is everything. OK, not really. The calendar is everything, but latitude is surprisingly important. But I get ahead of myself.

I think most everyone can agree that a sunny day is better than a cloudy or dark one. We may not be sure why, but this seems to be the consensus. And there has been a fair bit of study on this phenomenon. As is often the case though, there are many confounding factors in assessing why we feel better, happier with more sunlight. Is it the number of hours of light? The intensity or wavelength? Are there other predisposing factors, such as underlying depression? And, if this is all true, what's the biologic mechanism at play?

It seems that there are more than a few chemicals involved. More sunlight produces more serotonin, the happy molecule. Less serotonin=less happy. As you know, many antidepressants work through increasing serotonin. Autopsy studies and animal studies confirm higher levels of serotonin during the summer when there is more daylight.



Getty

Hours of sunlight also correlate with fluctuating levels of melatonin, in a cumulative fashion: higher at the end of the day, lower at the start. This may not be directly responsible for feeling good but, trust me, higher levels of endogenous melatonin providing a good night's sleep will make anyone feel better the next day. I doubt anyone here will be offended, but this may be why night-shift nurses are a tad grouchy, as I've recently been reminded. Sleeping all day and working nights is not what our physiology was built for.

Many people have some underlying tendency toward melancholy or even depression. And for a subset of those, seasonal changes in affect are specifically correlated to hours of sunlight. Colloquially known as Seasonal Affective Disorder, I would submit that to some degree or another, a large part of the population manifests SAD at this time of year. The long-standing feud over daylight savings time is in many ways an effort to minimize SAD, since very few want to leave work at the end of the day in darkness. It's pretty depressing. Even if it isn't mid-December, it is possible to be depressed any time of year when for extended periods the sun isn't out. Rain and clouds for a few days will definitely have an effect on me no matter what time of year, and the typically overcast weather in Philadelphia during the winter makes it all the worse.

And now, as promised, we'll return to latitude. We know that during the winter in the northern hemisphere higher latitudes have shorter days and at some point the sun doesn't even rise at all depending on where you are. Somehow though, I've always thought of that as some bizarre extreme that involves polar bears, that you wouldn't really experience that in the United States.

Aside from perhaps northern Alaska that's true, but you don't have to trek thousands of miles to notice the relationship of latitude and daylight. As part of my transition to retirement, I now have a residence in Florida as well as Philadelphia. And during the winter, I travel between the two regularly. It's not that far a trip, about 1,000 miles as the crow flies. I quickly noticed an interesting phenomenon, however. In the evening at this time of year, it's totally dark up north by 6 p.m., but in Florida the sun has over another hour left. And let me tell you, living that difference is pretty magical. Latitude and better weather certainly earn Florida its nickname as the Sunshine State. Unfortunately, especially this time of year, it's not always sunny in Philadelphia. ◀

This article has no commercial sponsorship.

Dr. Blecher is an attending surgeon at Wills Eye Hospital.

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

304 BINGO CARDS

Inspired by a real patient with Wet AMD.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

PROVEN VISUAL OUTCOMES AT YEAR 1 IN THE VIEW STUDIES

Fewer injections with EYLEA Q8 vs ranibizumab Q4

Demonstrated in the largest phase 3 anti-VEGF trials completed to date in Wet AMD (N=2412)[1-3]

Proportion of patients who maintained vision (<15 ETDRS letters lost of BCVA) at Year 1 from baseline[1-3,*]

	Primary Endpoint (Year 1)	
	VIEW 1	VIEW 2
EYLEA Q4	**95%** (12.5 injections†)	**95%** (12.6 injections†)
EYLEA Q8‡	**94%** (7.5 injections†)	**95%** (7.7 injections†)
ranibizumab Q4	**94%** (12.1 injections†)	**95%** (12.7 injections†)

*Last observation carried forward; full analysis set.
†Safety analysis set.
‡Following 3 initial monthly doses.

Vision was maintained at Year 1 with ≈5 fewer injections with EYLEA Q8 vs ranibizumab Q4

EYLEA was clinically equivalent to ranibizumab.

VIEW 1 and VIEW 2 study designs: Two multicenter, double-masked clinical studies in which patients with Wet AMD (N=2412; age range: 49-99 years, with a mean of 76 years) were randomized to receive: 1) EYLEA 2 mg Q8 following 3 initial monthly doses; 2) EYLEA 2 mg Q4; 3) EYLEA 0.5 mg Q4; or 4) ranibizumab 0.5 mg Q4. Protocol-specified visits occurred every 28 (±3) days.[1] In both studies, the primary efficacy endpoint was the proportion of patients with Wet AMD who maintained vision, defined as losing <15 letters of visual acuity at Week 52, compared with baseline.[1]

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH WET AMD AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

ADVERSE REACTIONS

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

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc. **3.** Heier JS, Brown DM, Chong V, et al; for the VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006

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

03/2021
EYL.21.02.0019

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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EYL.20.09.0052

The ESCRS IOL Calculator

An update on the new IOL calculator that uses seven major formulas simultaneously.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

In the fall of 2022, the European Society of Cataract and Refractive Surgeons debuted a new tool on its website that aggregates major online intraocular lens calculators into one site. Using the free online tool, surgeons can input their data once and then easily compare the results of up to seven calculators, including the Barrett Universal II, Cooke K6, Evo, Hill-RBF, Hoffer QST, Kane and Pearl GDS.

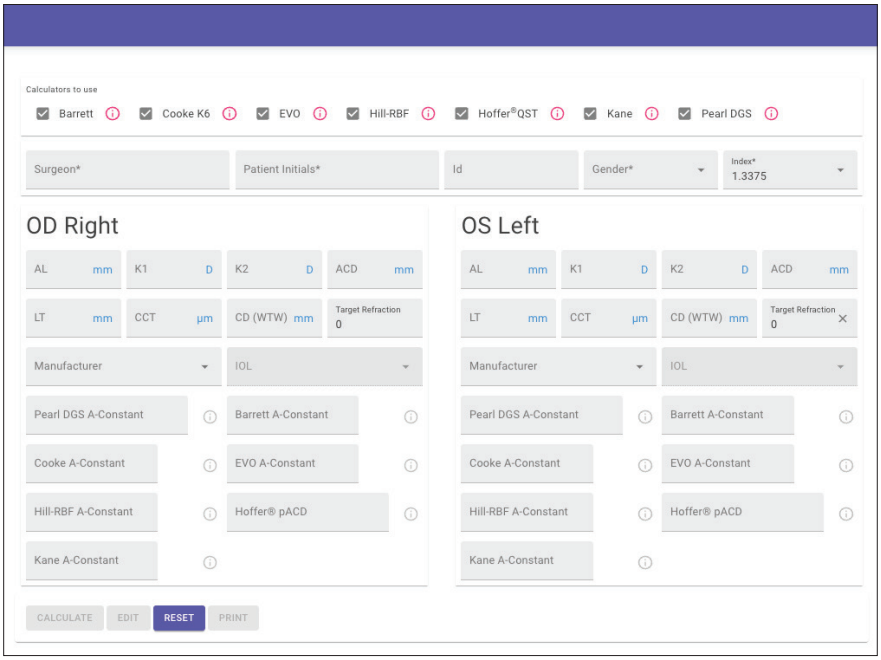
The idea originally came from Dante Luis Buosanti, MD, an ophthalmologist in Buenos Aires, Argentina. After reaching out to Kenneth J. Hoffer, MD, for permission to include his formula in the project, he and Dr. Hoffer approached ESCRS together to see whether the society would be interested in hosting this IOL calculation tool on its website. With the support of ESCRS board members, they secured permissions from the rest of the formula authors. The tool is available at iolcalculator.escrs.org.

How It Works

To create the calculator, the developers used a technique called web scraping, where bots extract information from other websites and bring it back to a single site. "Most of us are already familiar with web scraping to some degree," says ESCRS president Oliver Findl, MD, MBA, FEBO. "When you go to Google or other search engines to book a flight, you enter where you want to fly and the dates and times, and Google searches all the different airlines and looks for flights that fit your criteria. All of that information comes back to Google, and you're presented with your options, rather than having to go to each site individually and re-enter your information."

Not only is it boring and time-consuming to enter data into each calculator manually, he adds, but data entry mistakes may also occur at some point. "The ESCRS IOL calculator requires much less work and reduces the potential for error because you only have to enter the biometry data once," he says. "You receive a printout at the end with all of the formulae results next to each other. For example, it may say a 22-D lens of a certain manufacturer will have *x* predicted postoperative refraction for calculators one, two, three, four, etc. The more information we have the better."

Since the tool uses web scraping, any updates or improvements to the original calculators on their respective websites will automatically



ESCRS

With the ESCRS calculator, surgeons can obtain results from seven different formulas by entering the patient data only once. Experts say this helps to save time and reduce data entry errors.

This article has no commercial sponsorship.

Dr. Colvard is a surgeon at the Colvard-Kandavel Eye Center in Los Angeles and a clinical professor of ophthalmology at the Keck School of Medicine of the University of Southern California. **Dr. Charles** is the founder of the Charles Retina Institute in Germantown, Tennessee.

be seen in the ESCRS calculator. The ESCRS calculator also has a list of optimized IOL constants from IOLCon (iolcon.org) that can be used depending on the user's preference. "This ensures you're always using the most current IOL constant for a lens," Dr. Findl says. He adds, "We're very grateful to the authors of these formulae to let us bring them together on the ESCRS platform."

Strength in Numbers

Eduardo Viteri, MD, medical director of the Centro Oftalmológico HumanaVisión in Guayaquil, Ecuador, has tried the new ESCRS calculator in a few cases. He says the design is "elegant and user-friendly" with a report that's easy to interpret.

"Most cataract surgeons already have a well-proven biometric protocol," he says. "I usually calculate my cases with a Pentacam AXL, and the patients end up with a refraction close to the expected. What we want to avoid are refractive surprises that happen mostly in eyes that are on the extreme ranges of axial length or corneal curvature, or those with previous corneal surgery or pathology. Those are the cases where we'll take the extra time and effort to use multiple formulas or calculators. However, in those outliers we may end up with IOL power suggestions with a range of 1.5 or more diopters, and the surgeon may reach a conclusion that the calculator is of little use. So, the reality is that the [ESCRS] calculator will be mostly used in cases with the worse predictability, whatever the calculator or formula."

Having seven online calculators returning results helps with the informed consent process in these atypical cases, experts say. "If the calculators are in relative agreement with each other, we can tell the patient there's a high probability that we'll be really close to the refraction we're aiming for," Dr. Findl says. "If the results are all over the place, then we can inform the patient that their eye is difficult to calculate and that there's a greater chance we may need to do some secondary procedure to correct the refractive surprise."

Dr. Viteri agrees: "If the results are consistent among most of the formulas, I feel more confident that the postop result will be as expected. If I get dispersed results, I emphasize to the patient the high probability of a residual refractive error. In those cases, I usually choose an IOL on the myopic side of the average among calculated powers."

> **If the results are consistent among most of the formulas, I feel more confident that the postop result will be as expected.**
>
> ***—Eduardo Viteri, MD***

He ran an informal poll in ophthalmologist groups asking, "Which of the ESCRS IOL calculator formulas do you think is more accurate?" and found that, "among more than 100 respondents, the formula they trust most is Barrett, followed by Kane as a far second. The rest of the formulas aren't considered significantly better or more precise. I also found that as many as 40 percent of the responding surgeons haven't tried the ESCRS calculator."

Dr. Findl says a toric version of the ESCRS calculator is in the works with a tentative release date in the first quarter of this year. A post-refractive surgery calculator will be available in the summer of 2023. ◀

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WHICH LENS FOR WHICH PATIENT?

Cataract surgeons discuss the criteria they use when selecting a lens for a patient.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

Selecting the most appropriate implant for a patient can sometimes feel like being a matchmaker. Will the patient love the lens you recommend for years to come? Will the lens enrich their life and support them in the activities they love? Cataract surgeons say this process begins with a thorough conversation to get to know the patient. Here, they break down the IOL selection process and discuss several criteria they use when narrowing down their patients' options.

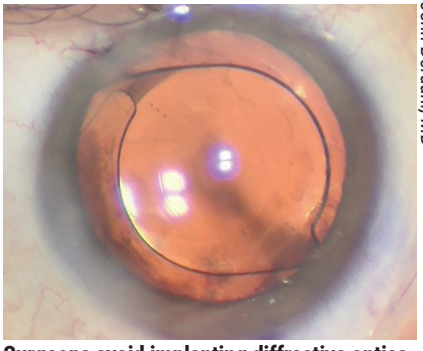
Patient Personality

Personality matters a great deal with selecting a lens for a patient because it's a good indication of how well they'll tolerate photic phenomena or be willing to sacrifice some visual quality in exchange for spectacle independence, experts say.

"When we talk about patient personality, we want to know things like whether the patient is anxious or whether they can tolerate a certain amount of uncertainty such as not knowing exactly what distance their vision will be in focus for their activities," says Y. Ralph Chu, MD, founder and medical director of Chu Vision Institute and Chu Surgery Center in Bloomington, Minnesota. "Can they adapt and accommodate change? Do they really understand what the limitations of each of the technologies presented to them are?"

Easygoing patients are often said to have more lens options than demanding or particular patients because they may potentially tolerate visual side effects better, but Dr. Chu points out that these stereotypes aren't always true. "When you get really into it, it may not be the patients you think who can't tolerate a certain technology," he says. "The stereotypically uptight, demanding patients may understand their needs really well, as well as the limitations of the technology. Many seemingly easygoing patients don't fully understand the technology. Don't fall into the trap of stereotyping. Be sure to get to know each individual patient."

Nevertheless, surgeons say they generally prefer not to implant diffractive optics in particular patients, those with great attention to detail, who notice all their symptoms or who can draw out their different focal points. "These patients will notice all the small decreases and increases in visual quality associated with multifocals," says Brian M. Shafer, MD, of Chester County Eye Care Associates in Malvern, Pennsylvania. "They're also likely to be bothered by dysphotopsias such as glare and halo."



John Berdahl, MD

Surgeons avoid implanting diffractive optics such as this trifocal in particular patients.

Near, Far, Wherever You Are

In addition to personality, experts

This article has no commercial sponsorship.

Dr. Berdahl is a consultant for Alcon, Johnson & Johnson Vision, RxSight and Zeiss. **Dr. Chu** is a clinical investigator for AcuFocus and Lenstec, and a consultant for Bausch + Lomb and RxSight. **Dr. Shafer** is a consultant and speaker for Alcon. **Dr. Farid** is a consultant for AcuFocus, Alcon, Bausch + Lomb, Johnson & Johnson Vision and Zeiss.

say the patient's visual goals are key for selecting the appropriate optics. How will they prioritize seeing at distance, intermediate and/or near? Do they want full spectacle independence or are they okay with wearing glasses for some activities? "We try to understand how patients want to use their eyes, and the best way to do this is by learning what the patient's daily life is like and what they want out of their vision," says John Berdahl, MD, of Vance Thompson Vision in Sioux Falls, South Dakota.

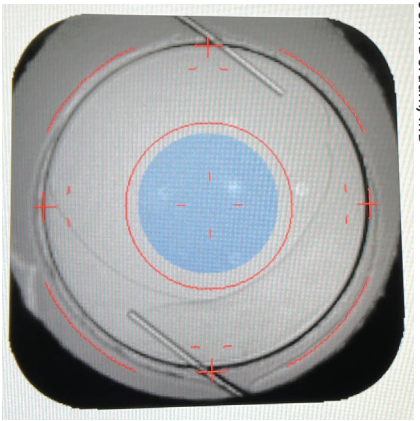
Dr. Shafer says that in general, hobbies are what people derive their happiness from, so prioritizing patients' abilities to exist most comfortably during their hobbies is important. "While there's no wrong choice for patients, there are better choices based on their hobbies and interests, so that helps us narrow it down to particular lenses," he says.

Here are some ways surgeons match patients' visual goals with IOLs:

Monofocal IOLs. Monofocal IOLs—including the Light Adjustable Lens and enhanced monofocals such as Eyhance and RayOne EMV—are designed to provide the highest quality vision at a single distance. They have the lowest side effect profile since they don't split light.

"Patients who want the best possible distance vision, such as those who enjoy hiking and taking in the views, are good candidates for a monofocal IOL targeting distance," Dr. Shafer says. "These patients will require glasses for near vision. Patients whose hobbies exist in the near range, such as reading or jewelry making, will do well with a monofocal lens targeted for near vision, especially if they're okay with wearing glasses for driving or watching TV. These patients would prefer not to wear glasses when doing near work."

Monovision is another visual strategy for certain patients that can provide some increased range of vision,



John Berdahl, MD

The Light Adjustable Lens is a good option for post-refractive surgery patients because it can be fine-tuned once the eye has healed, surgeons say.

though Dr. Berdahl points out that "it's one of the trickiest approaches for refractive surgery. With monovision, you're heavily dependent on the quality of vision in each eye to have a happy patient. We don't get the forgiveness that comes with both eyes targeted at the same focal point." He adds that the Light Adjustable Lens is helpful for achieving monovision since the second eye's target refraction can be adjusted and fine-tuned very precisely after the surgery.

"I've had good results using the Eyhance in a mini-monovision strategy," says Marjan Farid, MD, a clinical professor of ophthalmology and director of the cornea, cataract and refractive surgery program and the ocular surface disease program at UC Irvine School of Medicine. "Though it's not a presbyopia-correcting IOL, Eyhance can achieve a pretty nice range of vision with few to no side effects."

Multifocal IOLs. For patients interested in more spectacle independence and a greater range of vision than monofocals, multifocal IOLs such as the Synergy multifocal/EDOF hybrid or the PanOptix trifocal may be suitable. However, gaining sharp vision at multiple distances has its trade-offs due to the splitting of light.

"Because trifocals split light three ways, these lenses come with the expectation of glare and halos," Dr. Shafer says. "These lenses should be used sparingly in particular patients and those who are more likely to find those dysphotopsias bothersome. Trifocals are better suited for low-key individuals whose hobbies include looking into the distance and near work, such as a fly fisherman who needs both ranges of vision for fishing and tying flies up close."

Extended-depth-of-focus IOLs. EDOF lenses such as the Symfony OptiBlue and the non-diffractive Vivity create one elongated focal point to enhance a patient's range of vision. These lenses offer strong intermediate and distance vision, good near vision and few visual side effects.

Reducing visual side effects is an important innovation in lenses that offer greater range of vision. Vivity's non-diffractive optics stretch light to avoid light splitting, and the Symfony OptiBlue uses InteliLight technology, which is a combination of a violet-light filter, an echelette design and achromatic design. The violet-light filter blocks wavelengths that create the most light scatter to minimize visual disturbances; the echelette design reduces light scatter and halo intensity for easier digital screen viewing; and the achromatic technology corrects chromatic aberration for better contrast during the day and at night, the company says.[1]

Dr. Berdahl says EDOFs are good options for patients who want to decrease but not eliminate the need for readers and are interested in seeing at multiple distances, such as for watching sports on TV and in a stadium.

Sometimes two different IOLs is the best choice for a patient. Mixing and matching complementary multifocals or EDOFs may improve range of functional vision and decrease visual side effects. Combinations often include a low-add EDOF in the dominant eye and a high-add EDOF in the non-dominant eye; or an EDOF and a multifocal in the

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Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Important Safety Information (cont)

- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information about XIIDRA®, please refer to the brief summary of Prescribing Information on adjacent page.

†Pivotal trial data

The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0-4) and symptoms (based on patient-reported EDS on a visual analogue scale of 0-100).[1]

Effects on symptoms of dry eye disease: A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials.[1]

Effects on signs of dry eye disease: At day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 of the 4 studies.[1]

References: 1. Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **2.** Data on file. Fingertip Formulary® as of 07/2022. Novartis Pharmaceuticals Corp; July 2022.

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

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

1 INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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.

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. 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.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

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East Hanover, NJ 07936

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dominant and non-dominant eye, respectively.

"I've had a lot of success recently using the Symfony OptiBlue with InteliLight in the dominant eye and the Synergy in the non-dominant eye for patients who want excellent distance vision with full range," says Dr. Farid. "In general, I avoid mixing a diffractive with a non-diffractive optic."

Accommodating IOLs. In theory, lenses such as Crystalens AO and Trulign adjust as your eye moves, mimicking the natural crystalline lens. Dr. Chu says that these lenses offer some extended range of vision for patients who are okay with wearing a thin pair of readers to read fine print. "Accommodating lenses may be suitable for patients who may not tolerate the risk of nighttime dysphotopsias or who just don't want to take that visual side effect risk," he adds.

Dr. Farid says she doesn't often implant accommodating lenses because the final near point may be unpredictable. "Sometimes these lenses accommodate a little early in the eye and then you don't get as much range of accommodation," she explains. "I have more success with fixed multifocal EDOF lenses than the current accommodating lens. But though accommodating lenses aren't my primary choice, I'd consider one if a patient already had one implanted successfully in their eye; I'd match the lens in the other eye."

Value Determination

A patient's ideal implant for their visual goals isn't always a feasible option. While monofocal IOLs are usually covered with the cataract surgery by the patient's insurance, premium lenses are an out-of-pocket expense.

When finances present an obstacle, the choice of lens becomes a value determination, says Dr. Berdahl. "Patients must consider how much these lenses cost, and how much they're willing to pay for the additional freedom that comes from less dependence on glasses," he says. "In studies, quality of life has been shown to improve dramatically in patients who are less dependent on glasses and contact lenses after surgery. Patients' understanding of the value proposition is important. There's the cost of the procedure and sometimes the cost of the lens to consider."

Dr. Chu agrees: "Patients must understand that there's an elective portion to this as well as a medical portion. The more patients understand before surgery, the more empowered they are to make their own decisions and feel like they're part of the process."

Reading Point

Dr. Farid says she considers a patient's height when choosing an IOL. "The patient's stature indicates where their reading point will be," Dr. Farid explains. "A very tall patient's reading point will be farther out, so that patient might do better with an EDOF lens, as opposed to a very short patient, whose reading distance will be much closer. A shorter patient may do better with a multifocal lens to achieve better near vision."

Preop Refractive Error

"One of the major factors to consider in IOL selection, besides personality, is the patient's preoperative refractive error," Dr. Shafer says. "If you have a hyperopic patient, they typically appreciate any type of lens you put in there, because they're depending on glasses for things far away and up close.

"Moderate myopes (between -2 and -4 D) are used to taking off their glasses and being able to see up close," he continues. "They've basically got a telescope built into their eyeball. If you take away these patients' near vision, they'll be very upset with you because they're used to that superpower of not needing glasses to read.

"On the other hand, high myopes tend to wear glasses all the time unless they want to hold something about an inch in front of their eyes," Dr. Shafer says. "These patients tend to do well with different lens choices such as a monofocal set for near; an EDOF set for -1 D to give them a little bit of distance blur but more range up close; or a trifocal set for plano where they'll still get that 20/20 distance and near vision."

Young Patients

When faced with a young cataract patient or young refractive lens exchange patient, Dr. Shafer says he thinks about what might happen in the next 20 or 40 years of the patient's life when he selects an IOL.

"I implant many more EDOFs than diffractive multifocals for a number of reasons," he says. "My patient population tends to be very observant and therefore doesn't enjoy the glare and halos associated with diffractive optics.

"I also do a decent number of secondary IOLs for dislocated lenses, and some of these lenses are in patients who are 40 years out from cataract surgery," he continues. "I think a lot about what happens when we're doing cataract surgery on younger patients—what if their lenses dislocate? Well, if they have a diffractive multifocal lens that dislocates more than a millimeter, you're in big trouble. That patient isn't going to see nearly as well. But, if an EDOF dislocates a little bit, there's more wiggle room.

"Refractive lens exchange patients may have a perfectly healthy eye at the time," he adds, "but we don't know what their eye will look like 20 years from now. They may go on to develop an epiretinal membrane or macular edema or diabetic retinopathy. We shouldn't use diffractive lenses in patients with those conditions. If the patient were to develop one of those conditions, I'd feel a little responsible for having put a diffractive multifocal in their

eye. Such a patient would still be able to function fairly well with an EDOF—particularly a non-diffractive one—even if they developed some posterior pathology."

Ocular Comorbidities

"Intraocular lenses work best in pristine eyes, but many eyes simply aren't," says Dr. Berdahl. "It's incumbent on the surgeon to make sure that the patient knows their eye isn't perfect and that that'll limit their lens options."

Surgeons says that when they assess ocular health for IOL suitability, some of the problems they look for include ocular surface dryness or meibomian gland debris; astigmatism, corneal dystrophies or corneal irregularities due to scarring or trauma; and diseases such as glaucoma, macular degeneration or epiretinal membrane in the posterior segment.

"If the eye is healthy, the patient has many lens choices, but having corneal or retinal pathology really puts a patient in the monofocal lens category right off the bat," Dr. Farid points out. "Multifocality is sensitive to any comorbidity or irregularity, so it's best to avoid these lenses in eyes with pathology."

Dr. Shafer agrees, noting that regardless of the ocular condition, patients can still have their astigmatism managed. He points out that "patients with retinal pathology inherently have less activity of the photoreceptors and therefore the photoreceptors are already starving a little for light. Implanting a lens that splits light into multiple focal points means there's less light for each focal point, and that's not ideal.

"I don't put diffractive lenses in patients who have any sort of posterior pathology or any prior retinal detachment," he says. "That being said, patients with posterior pathology do just fine with a monofocal lens and generally do pretty well with an EDOF lens as well."

In terms of corneal pathology, Dr. Shafer says this is tricky to manage because the corneal pathology scatters the light before it even hits the IOL. "Then, you have poor-quality light hitting the lens and poor-quality light coming out of the lens," he says. "It's like 'garbage in, garbage out.' I approach patients with corneal pathology different than those with posterior pathology, because when you have posterior pathology, the retina isn't sensing the light properly. With corneal pathology, the light isn't focused properly. I tend towards monofocal IOLs for patients with corneal pathology."

Experts say some of the most challenging cases are patients with ocular surface instability and those with pathology but who also strongly desire spectacle independence. "When patients have ocular surface disease, we have to take our time and ensure we've stabilized the ocular surface and tear film before taking measurements and finalizing our IOL choice," Dr. Farid says. "Ocular surface disease can really impact biometry and topography. The more the preoperative biometry and topography measurements match, the more confident we are in the lens selection; the less they match, the more inconsistent they are, the trickier it is to select the lens power.

"For these cases, I'll put the surgery on hold to make sure the patients are getting the proper treatment for tear film dysfunction and ocular surface disease," she says. "We might bring them back twice or even three times to make sure their measurements are making sense and their ocular surface is clear. We'll get better outcomes and better patient satisfaction this way."

"I find the trickiest IOL selections are patients who hate wearing glasses and want full spectacle independence but also have pathology," Dr. Shafer says. "These patients require extra chair time and additional preoperative visits to determine 1) whether they can tolerate the loss of near vision and be okay with the fact that they can't see up close as well as they used to; 2) whether they could possibly tolerate a little bit of monovision; and 3) whether they could potentially tolerate both eyes being set for -1 D and having a slight distance blur but still have their full range of close vision. These are really tricky conditions because of all the preoperative counseling and because the patient has to sacrifice something. There's no perfect lens out there."

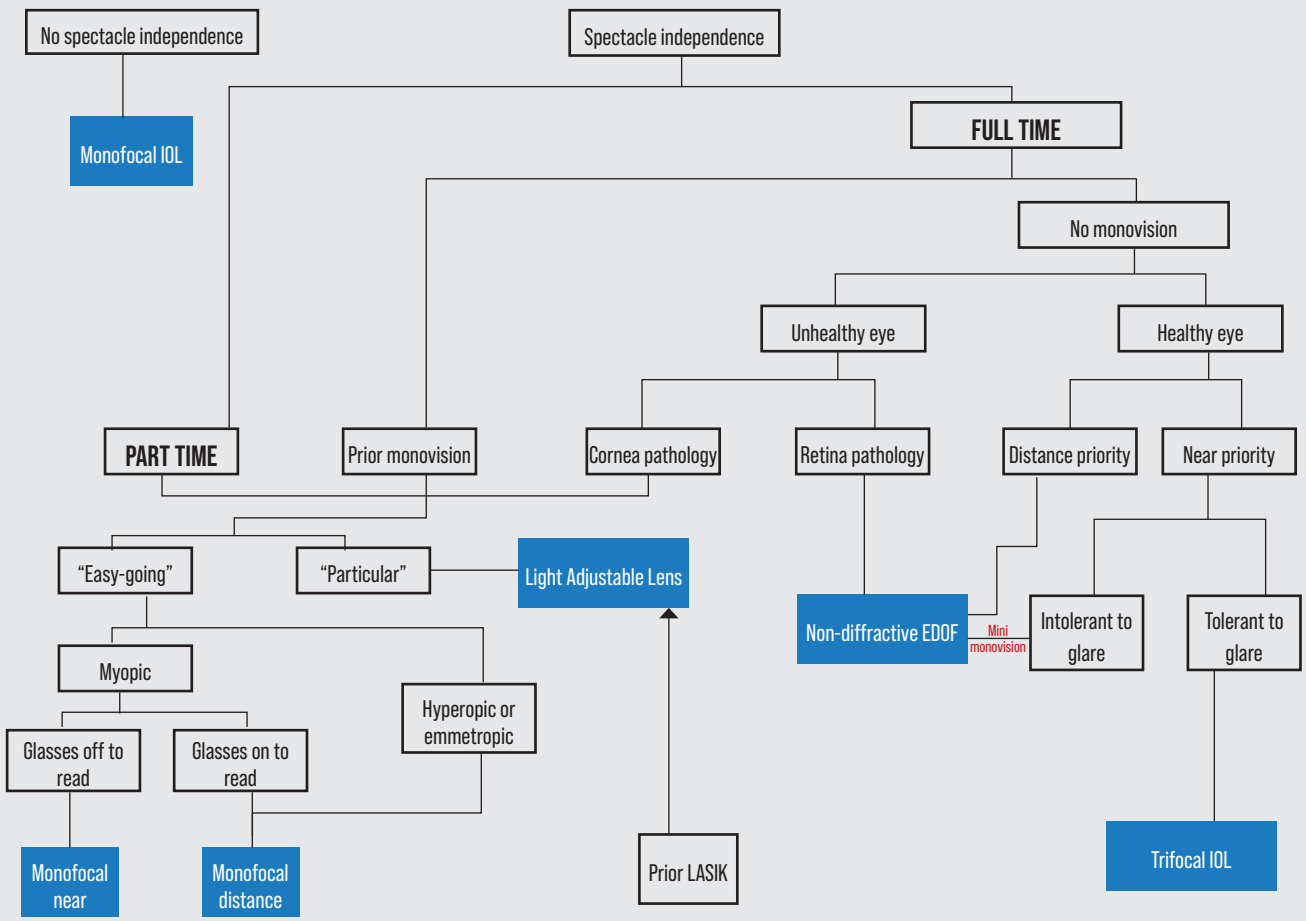
Previous Refractive Surgery

"What surgeons are mainly concerned about is that a surgical procedure on the cornea such as LASIK or RK can change the shape of the cornea and lead to a small loss of contrast sensitivity that may not have been measurable when the patient was younger and had just had corneal refractive surgery," says Dr. Chu. "When we add a lens implant that has multifocality but also decreases quality of vision or contrast sensitivity, the two stacked together can cause a situation where the patient is unhappy with their lens implant results."

Dr. Shafer says post-refractive surgery patients fall into two categories: those who have normal topography (where there's no reason to believe their eyes won't focus light properly) and those who have irregular astigmatism (whose eyes won't refract light properly). "The patients in the latter category with irregular astigmatism fall into the same category as the patients with corneal pathology," he explains. "No matter what type of lens the light hits, it's going to come out wrong."

For post-refractive patients who can still refract light normally, Dr. Shafer says he prefers to use the Light Adjustable Lens. "The reason I prefer the Light Adjustable Lens is because we can fine-tune it," he says. "Almost all of our formulas for measuring IOL power assume the patient hasn't had refractive surgery. Now there are newer formulas that

AN IOL SELECTION FLOWCHART



Brian M. Shafer, MD

do, but they're not perfect—and even on our best days, we can only be within half a diopter of our targeted spherical equivalents in post-refractive eyes 60 percent of the time. The other 40 percent of time, we get it wrong."

"The Light Adjustable Lens is the only lens where I can guarantee patients a certain outcome because we can make fine adjustments on both the astigmatism and the range of vision," Dr. Farid notes. "I like to do these surgeries bilateral, same day. Patients do very well with a bit of mini monovision, as there is a degree of extended range of focus that the IOL has, especially after the first adjustment."

Dr. Chu also uses the Light Adjustable Lens in patients whose refractive outcomes are unpredictable due to past corneal refractive surgery. "This lens works well in patients who want precise vision and some extended depth of focus. To be a candidate for the Light Adjustable Lens, patients must have an adequate pupil size of about 6 mm or more. Having adequate pupil size with the light adjustable lens is important for adjusting the entire surface area of the lens, in our experience," he says. "We assess the patient beforehand to ensure their pupils dilate sufficiently."

He says that pupil size is important for multifocal and aperture-type lenses as well. "If the pupil is smaller than the central zone of the optic, the patient may not get as much effect from the IOL's multifocality, depending on the type of lens," he notes. "Understanding pupil size in relation to a lens is key for determining patient suitability for a lens in the decision-making process."

"My approach is to ask the patient if they were happy with their vision right after their refractive surgery," says Dr. Berdahl. "If they were, then it's likely their quality of vision is good. If the patient has irregular astigmatism on topography, a gas-permeable over-refraction as part of the cataract workup is very helpful. If the vision improves with gas-permeable over-refraction, then the cornea is contributing to the issue and good uncorrected vision may not be possible.

"My go-to lens in post-refractive surgery patients is the Light Adjustable Lens because of the inherent unpredictability associated with prior refractive surgery," he continues.

Y. Ralph Chu, MD

Some surgeons say they're looking forward to offering the small-aperture IC-8 Apthera to their patients with irregular corneas.

"The LAL is adjusted after the patient heals from surgery, so the treatment is based on the manifest refraction after the patient's healed. We do use multifocal and EDOF lenses in post-refractive patients, however these patients need to be counseled because it's more likely that they may not get the intended target, they may have visual disturbances or their lenses have a higher likelihood needing to be removed. Also, it can be more difficult to perform a refractive surgery enhancement on top of prior RK, LASIK or PRK."

New Technology

Some surgeons say they're looking forward to offering patients two new lenses:

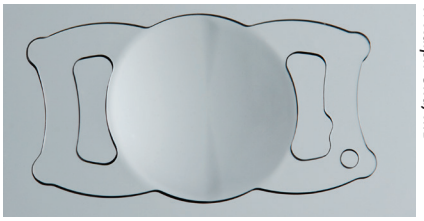
IC-8 Apthera. FDA-approved in July 2022, this small-aperture lens from AcuFocus uses pinhole technology to achieve an extended depth of focus by filtering out peripheral defocused light and aberrated light.[2] It's suitable for patients with as much as 1.5 D of corneal astigmatism. Experts note that one trade-off with pinhole optics is a reduction in monocular contrast sensitivity.

In the U.S. Investigational Device Exemption study, 453 subjects received either the Apthera in one eye and a monofocal or monofocal toric IOL in the fellow eye (n=343); or monofocal or monofocal toric IOLs in both eyes (n=110). According to the study, Apthera-treated eyes maintained 2 D of extended depth of focus and provided 0.91 D of additional range of vision over the control group at a 0.2-logMAR threshold, which AcuFocus notes exceeds the 0.5 ANSI criterion for EDOF IOLs. Compared with the control group, the treatment group demonstrated equivalent UDVA; statistically better intermediate and near vision; and comparable binocular contrast sensitivity in photopic and mesopic conditions.[2]

"This approval opens up a lot of potential for enhanced mini monovision in patients, where we'd implant a monofocal lens set for distance in the dominant eye and a pinhole optic in the non-dominant eye to offer extended depth of range," Dr. Farid says. "We're looking forward to offering this option to our patients for presbyopia correction but also for irregular corneas."

Dr. Shafer agrees, noting that though the Apthera is approved for presbyopia correction, "the majority of us aren't looking at the lens in that light. We're looking forward to having this lens available for our patients with highly aberrated corneas. As I mentioned before, with these corneas, it's 'garbage in, garbage out.' But a pinhole optic will take the garbage that comes in, focus it through a small aperture, and allow only that already focused light to make its way through to the retina. So, this is a great option for patients who are post-RK, post-penetrating keratoplasty or have active keratoconus or other forms of ectasia. I have a couple of patients already who are waiting for me to call them as soon as I have access to this lens."

ClearView 3. Dr. Chu was a clinical investigator for the Apthera as well as another new addition to cataract surgeons' armamentarium: the recently rebranded ClearView 3 asymmetric segmented multifocal lens (formerly the SBL-3) from Lenstec, which was also FDA approved in July 2022. The lens is available in 0.25-D power increments and features "a true 3 D sector-shaped add with a seamless transition zone between the distance and near segments," according to Lenstec.[3]



Y. Ralph Chu, MD

The ClearView 3 segmented IOL can be rotated to reduce dysphotopsias while maintaining distance and reading vision, says Y. Ralph Chu, MD.

In the FDA clinical trial, 495 patients received either a conventional monofocal IOL or the ClearView multifocal in at least one eye. The ClearView provided improved near visual acuity and comparable intermediate and distance vision at six and 12 months after surgery. According to patient questionnaires, those who received the ClearView IOL reported lower usage of readers or near-vision contact lenses than those who received monofocal IOLs.[4]

"We're still learning the best patient profile to offer these bifocal segmented lenses," says Dr. Chu. "But an advantage is that patients already understand the distance and reading segments of bifocals. The ClearView offers the range of focus of a multifocal lens with a little less dysphotopsia, as well as the ability to potentially reduce this without having to do an explant. If a patient has dysphotopsias, the segmented lens can be rotated, and oftentimes that will reduce or eliminate dysphotopsias and still preserve the ability of the lens to give distance and reading vision. So, that's an exciting option to have." ◂

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2. Acufocus announces FDA approval for the IC-8 Apthera intraocular lens, the first and only small aperture lens for cataract surgery. https://acufocus.com/press/aptheraiolfdaapproval. Accessed December 8, 2022.
3. ClearView 3 multifocal IOL. https://www.lenstec.com/clearview3.html. Accessed December 8, 2022.
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CATARACT SURGEONS EMBRACE NEW OPTIONS

Cataract surgeons who responded to our annual intraocular lens survey are both hewing to their tried-and-true options and leaving the door open for new lenses, too.

WALTER BETHKE
EDITOR IN CHIEF

As cataract surgeons know, their surgery relies heavily on technique, but also on technology, especially intraocular lenses. On our latest survey of IOL preferences, many surgeons seem to be sticking to the lenses that provide the solid postop results they're used to getting, but some are branching out into new options, such as premium lenses that have recently been approved in the United States.

This is just one of the findings from this year's e-mail survey on IOL preferences. This time around, 25 percent of the 10,540 recipients on *Review*'s e-mail list opened the message, and 58 surgeons took the survey.

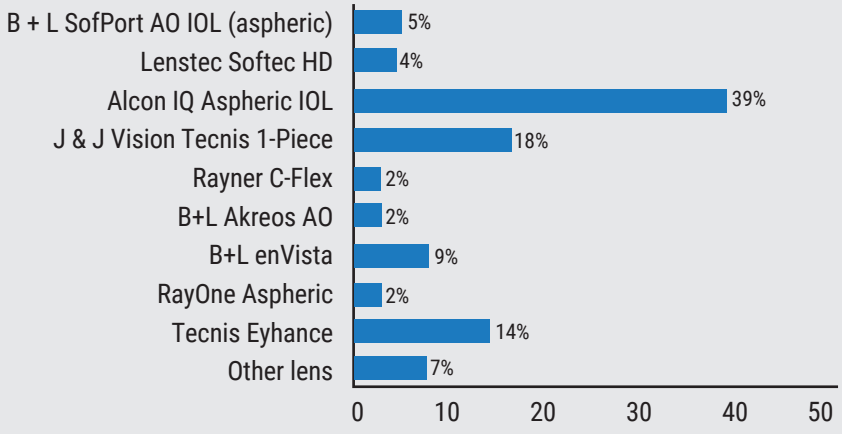
To read about your colleagues' impressions and usage patterns of both the stalwarts and the new upstarts in the IOL arena, as well as their views on other intraocular lens technologies, read on.

Premium Lens Options

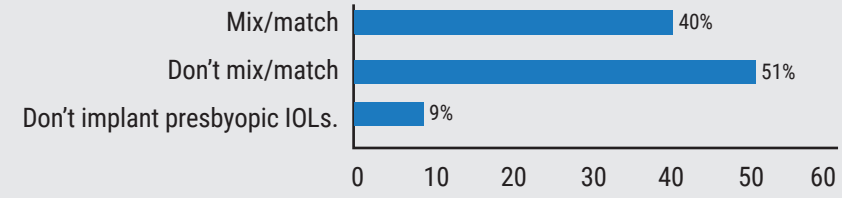
Surgeons on this year's survey still seem to be leaning toward trifocal options, but newer additions to the premium intraocular lens marketplace are turning heads, as well.

The most popular premium lens on the survey (some surgeons chose more than one option) is the Alcon PanOptix Trifocal, used by 52 percent of the respondents. In terms of the average number of PanOptix lenses implanted per month, the

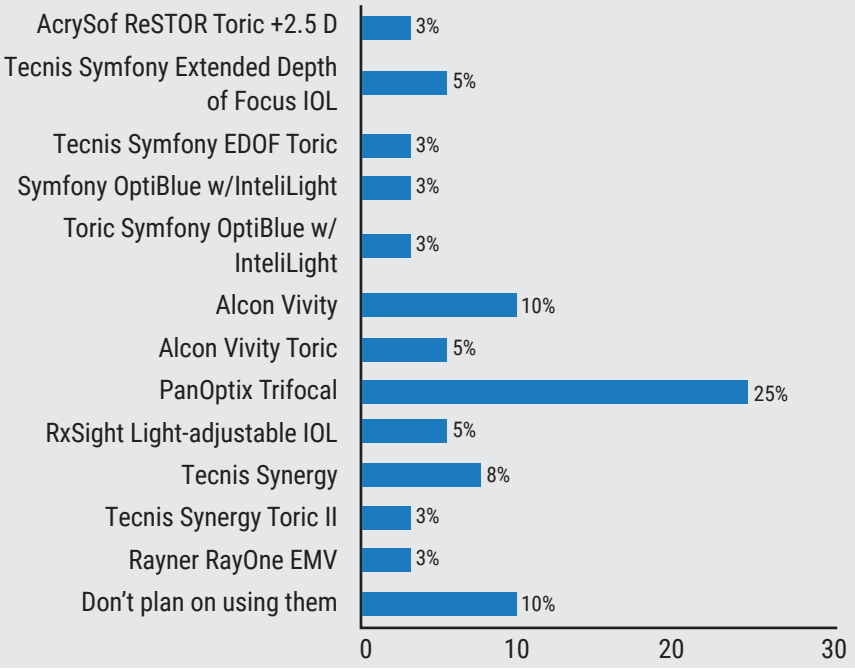
Preferred Non-premium IOL for Most Cases



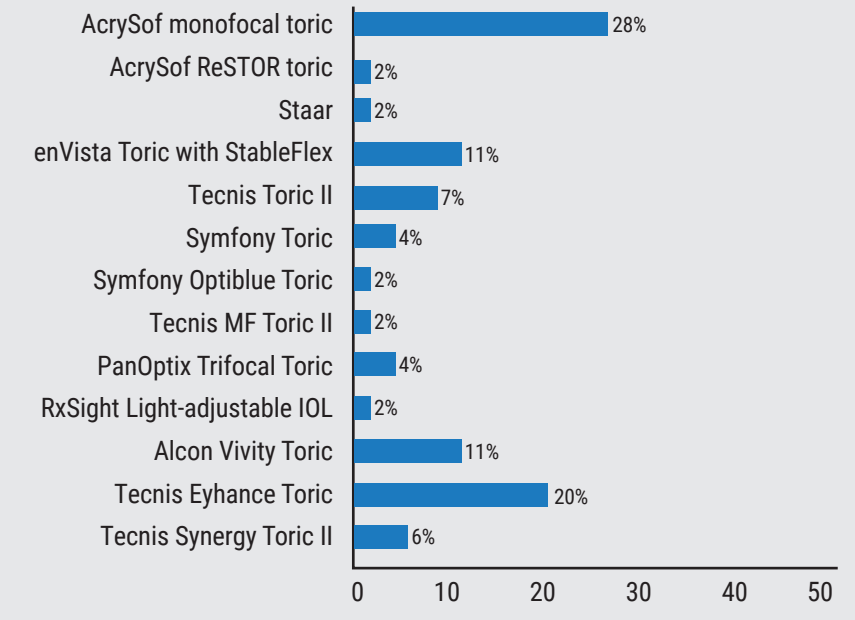
Surgeons Who Mix/Match Presbyopic Lenses



If Surgeons Get into Presbyopic Lenses, Which Will They Start With?



Preferred Toric IOL



users say they implant about eight lenses on average, at an average charge for the patient of $2,945 per lens. Next in line was the toric PanOptix, used by 47.9 percent of respondents (average number of PanOptix torics implanted per month: 7; average charge per lens: $3,172).

Paula Young, MD, of Alexandria, Virginia, says she implants the PanOptix but that there's a bit of room for improvement in terms of "associated dysphotopsias and lengthy chair time." A Kentucky surgeon also likes the PanOptix, but wishes it gave "a better range of vision," he says, adding, "It still has unwanted halos." A surgeon from Washington who primarily uses the PanOptix says he's "somewhat satisfied" with the IOL, adding, "I dislike the reduced contrast sensitivity and the increased expectations from patients that come with the expense of the lens." Jonathan Adler, MD, of Bradenton, Florida, likes the PanOptix, saying it "gives a great range of vision." He notes, however, that it "needs to be implanted in eye without an epiretinal membrane, and not in post-refractive eyes."

Next in line is the Alcon Vivity IOL, used by 39.6 percent of respondents (average number implanted per month: 6; average charge per lens: $3,164). Close behind is the Vivity toric, used by 37.5 percent of the surgeons (average number implanted per month: 9; average charge per lens: $3,083). Dr. Adler says Vivity "gives excellent range of vision for post refractive patients." Baltimore surgeon Ismail A. Shalaby says he likes the Vivity, but he would "love better near vision" from it.

Another popular lens was the Tecnis Synergy, used by 31.3 percent of respondents (average number implanted per month: 5; average charge per lens: $2,798).

Fifteen percent of the surgeons use the Rayner RayOne EMV IOL (average number implanted per month: 8; average charge: $1,748), and 10 percent implant the Crystalens (average number implanted per month: 1; average charge: $1,500).

In terms of the new offerings in the premium space, 19 percent of the surgeons use the Symfony OptiBlue with InteliLight (average number implanted per month: 4; average charge per lens: $2,924). The Lenstec Clearview 3 Multifocal is used by 13 percent of the respondents and 10 percent implant the new AcuFocus IC-8 Apthera (the surgeons choosing the Clearview and the Apthera didn't provide data on lenses per month or how much they charge).

IOL Attributes Surgeons Value (1= least important, 8=most important)

Attribute	Average score
Asphericity/neutral asphericity	6.22
Blue-light blocking	5.51
Violet-light blocking	5.3
Toric Design	5.08
Extended Depth of Focus Design	5.08
Edge design to decrease PCO	5
Bifocal Multifocality	4.82
Trifocality	4.76
Ability to adjust IOL power post-implantation	3.83

Toric IOLs

For tackling astigmatism, 28 percent of the surgeons say they use the AcrySof toric the most, followed by 20 percent who prefer the Tecnis Eyhance toric. Eleven percent of the surgeons use the Bausch + Lomb enVista Toric with StableFlex.

"It's reliable, and easy to center and adjust," says a surgeon from Washington about the AcrySof toric.

Bruce H. Cohen, MD, of St. Louis, prefers the Eyhance toric, saying, "It works well, with a broader range of focus and no glare."

[The enVista Toric] IOL's rotational stability is improved over lenses I previously used," says a surgeon from Virginia.

The rest of the toric lens results appear in the graph on the facing page.

Monofocal Mainstays

Surgeons also shared their thoughts on the bread-and-butter lenses for cataract surgery: the monofocals.

Thirty-one percent say they prefer the Alcon IQ Aspheric IOL, followed by the J&J Vision Tecnis One-piece (18 percent). The next most popular lens is the Tecnis Eyhance (14 percent), followed by the B+L enVista (9 percent).

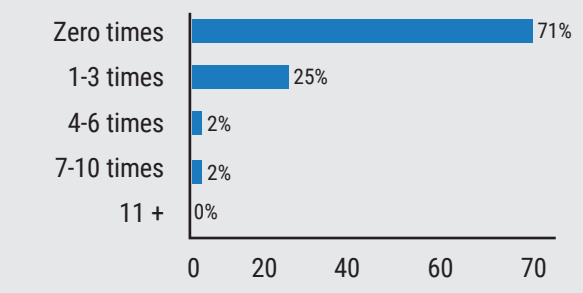
A surgeon from Washington uses the AcrySof monofocal the most, saying, "I like that it is time-tested, easy to load and has delivered reliable outcomes for many years. I dislike that it is yellow-tinted."

A doctor from Georgia prefers the Tecnis One-piece. "I like the clarity, color appreciation by patients, and lack of glistenings," he says. A surgeon from California likes to use the Eyhance, noting, "[It's part of the] Tecnis line: same A constant across the entire platform. It's an easy-to-use, pre-loaded PCIOL."

A surgeon in the enVista camp says he prefers it because it "opens cleanly, looks great on postop day one and there are no glistenings."

All of the monofocal results appear in the graph on page 35.

How Often Surgeons Suture an IOL in a Year



Phakic Lenses

Only 28 percent of the respondents say they implant phakic IOLs. For those that do, all of them use the new EVO/EVO+ Visian (either the toric or non-toric version).

Manhattan surgeon Jimmy Hu says the EVO is a "great option for many patients, but it requires a lot of patient counseling." He adds, "It's also more involved surgery compared to LASIK/SMILE/PRK, and the patient needs to be aware of that. However, for high myopes, quality of vision is much better than LASIK/SMILE/PRK (because of fewer higher-order aberrations), and many of these patients are super happy."

"They seem to be a niche technology that could be great for the right patient, but aren't a first-line option for most patients," says a doctor from Washington.

Suture Situations

For those rare situations in which there's not enough support for an IOL in a patient's eye, surgeons discussed their thoughts on suturing techniques. The frequency of having to suture a lens appears in the graph at the bottom of this page.

A surgeon from North Carolina says in his experience, the usual causes for the instability are "floppy-iris syndrome and poor zonules." A Pennsylvania surgeon cites "no bag support," and adds that he scleral fixates.

"I don't suture a lens to the iris, but I do perform scleral-fixated IOLs," opines Dr. Hu. "I prefer either the Yamane technique using a Zeiss CT Lucia 602 lens, or Akreos AO60 fixation to the sclera with Gore-Tex sutures. I don't perform iris fixation because even though it's a technically easier surgery, the prolene sutures often break in about 10 years, requiring additional surgery." A Texas surgeon agrees, saying, "I refer to retina, since scleral-sutured IOLs are better than iris-sutured lenses." ◀

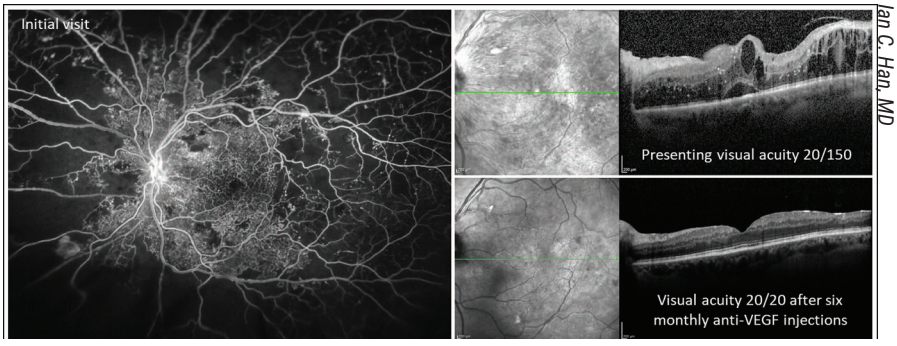
TREATING PROLIFERATIVE DIABETIC RETINOPATHY

Whether it's with anti-VEGF or PRP, patients' outcomes may depend on their access to care and ability to follow up.

LIZ HUNTER
SENIOR EDITOR

Managing patients with diabetic retinopathy can be a challenge. Not only do some patients remain asymptomatic and unaware of the advancing disease, many are not even going for regular eye exams. Diabetic retinopathy is the number one cause of blindness in American adults ages 20 to 74, and although it's recommended that diabetics receive annual eye exams, more than 50 percent of those with DR don't receive necessary screening.[1]

Understanding this patient population is integral to treating their disease, and that includes comorbidities and risk factors that could contribute to their outcome. We spoke with several retina specialists about their standards of care for proliferative diabetic retinopathy specifically, how they determine if a patient is best suited for anti-VEGF or panretinal photocoagulation and what they suggest to improve patient trust and follow up.



Ian C. Han, MD

Figure 1. Images from a male patient in his 30s with poorly controlled type 2 diabetes (hemoglobin A1c >12%) and no prior eye care. Fluorescein angiography on initial visit showed extensive areas of peripheral non-perfusion with fronds of neovascularization (left eye shown). OCT showed severe center-involving diabetic macular edema (top right) which responded well to intravitreal anti-VEGF (aflibercept) injections (bottom right). By one year after presentation, he was 20/20 in both eyes with an A1c <7% due to improved adherence to diabetes care and better systemic glucose control.

PDR Symptoms and Screening

Proliferative diabetic retinopathy distinguishes itself from non-proliferative diabetic retinopathy in its severity. PDR's tell-tale sign is neovascularization, brought on by poor glycemic control, high blood pressure, high cholesterol and other chronic health issues. When left untreated, the risk for retinal detachment increases.

Vascular damage often occurs more in the peripheral areas of the retina, says Jason Hsu, MD, co-director of retina research at Wills Eye Hospital, assistant professor of clinical ophthalmology at Thomas Jefferson University Hospital in Philadelphia, and a managing partner of Mid Atlantic Retina.

"These patients may go to their general eye doctor with little or no symptoms or maybe just for a pair of glasses and are incidentally found

This article has no commercial sponsorship.

Dr. Han reports no disclosures. **Dr. Hsu** is a consultant for IvericBio, Gyroscope Therapeutics and Bausch + Lomb, and receives grant support from Genentech/Roche, IvericBio and Aldeyra Therapeutics. **Dr. Lim** is a consultant for Alcon, Aldeyra Therapeutics, Allergan, Chengdu Kanghong, Eyenuk, Genentech, IvericBio, Novartis, Regeneron and Santen.

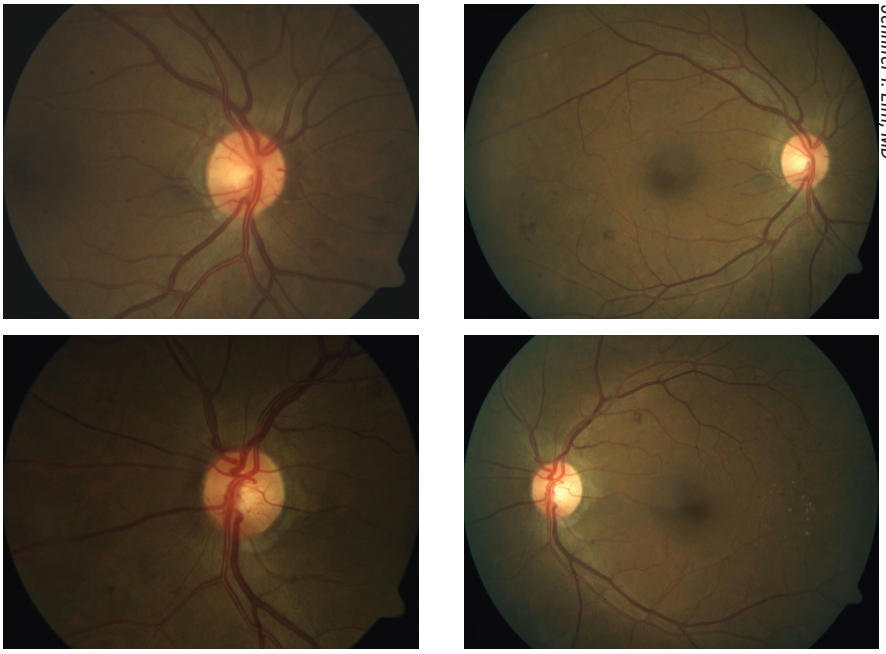
to have massive neovascularization. Their eye doctor may say, 'Wow, you have a lot of damage' or 'You're at high risk of losing your vision,' and it's not uncommon that they don't believe the doctor because their vision is still pretty good," he says. "If they do present with symptoms, they may include new onset of floaters from some vitreous hemorrhage. Those are very common scenarios for how these patients are first diagnosed. Another thing that can occur in all diabetics where there's proliferative or non-proliferative diabetic retinopathy is diabetic macular edema, and that would cause some more central blurring and could be more symptomatic as well."

Diagnosing asymptomatic patients may take some careful screening, advises Ian C. Han, MD, an associate professor in the department of ophthalmology and visual sciences at the University of Iowa Hospital and Clinics.

"For me, screening still starts with listening to the patient and obtaining a careful history," Dr. Han says. "For example, if you have somebody who's just coming in for a new eye examination, but they've had a diabetes diagnosis for 15 years, your initial examination is already alert to the strong possibility of PDR. I often tell the residents and fellows to default to the assumption that the patient has PDR—and prove to yourself on clinical examination that they don't—otherwise you might miss signs of the disease."

Different imaging modalities include baseline fundus photography and OCT, as well as fluorescein angiography and OCT angiography. "PDR is kind of tricky because, on an OCT, you might not see a whole lot," Dr. Hsu says.

Dr. Han agrees. "PDR patients actually have a pretty bland-appearing fundus; you may not see a ton of hemorrhages and such. Someone in a routine eye clinic may see a patient with 15 to 20 years of poorly controlled diabetes and see a dot hemorrhage here or there and assume that they only have minimal disease because blood is the most apparent fundus finding when in fact, it's a PDR with neovascularization that is missed," he says.



Jennifer I. Lim, MD

Figure 2. This patient presented with PDR in both eyes, shown in the preop fundus images taken in April 2017 (left column). After treatment with an anti-VEGF, the PDR is no longer apparent in fundus images one month later (right column).

"Now, if you're getting a wider field OCT, then you can sometimes pick up neovascularization along some of the arcades and over the optic nerve," Dr. Hsu says. "The neovascularization often forms hyperreflective membranes, almost like an epiretinal membrane but often with greater separation above the plane of the retina or the optic nerve. One thing that's helpful to pay attention to is the near infrared image of the macula that's used to correlate where the OCT cut is going through. Neovascularization on the near infrared image usually looks dark and obscures part of the vascular arcades or the optic nerve. While that's not 100 percent proof that it's neovascularization, it can clue you in and tell you to look more carefully."

"With ischemia and vascular remodeling, intraretinal hemorrhages may be less prominent, so ophthalmologists may miss some of the more severe or more advanced findings that fall in the category of PDR unless you study the retinal blood vessels carefully on exam or imaging," Dr. Han says, with a recommendation not to over-rely on technology to make the diagnosis. "Clinical context is still really important. Even with modern technology, some subtle vascular abnormalities may not be as apparent unless you go looking for them or they're below the resolution or the quality of your image," he says.

Treatment Decisions and Debates

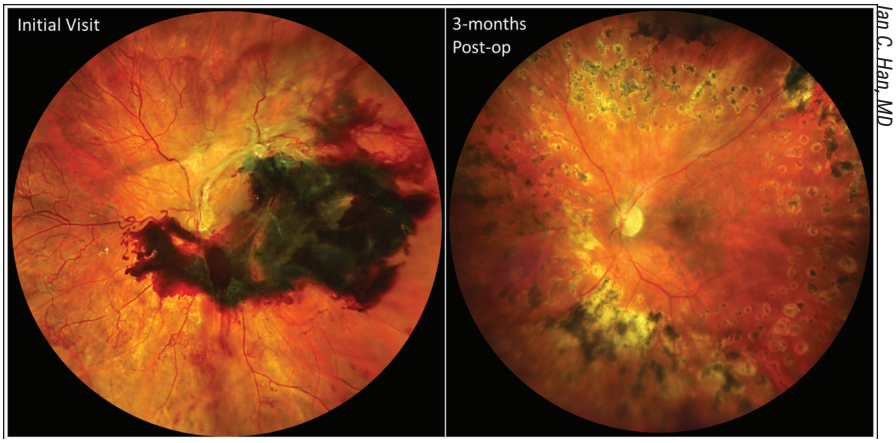
Treating PDR depends on its severity. "Laser is the 'traditional' therapy that has been around for decades," says Dr. Hsu. "In this situation, we do panretinal photocoagulation. We create a pattern of laser that is spaced out by about one spot width and typically staying at least 1 to 2 disc diameters away from the major arcades and the optic nerve, so as to not interfere quite as much with the patient's perception of their peripheral vision." A 1976 study was the first to show PRP's benefits in lower-

ing the risk of vitreous hemorrhage and reducing the risk of vision loss by 50 percent.[2]

"I definitely try to start with PRP first when I can, but the problem is, being in a retina referral practice, the patients are coming in because they have vitreous hemorrhage. When there's vitreous hemorrhage present, the laser isn't effective because the blood in the vitreous scatters the laser beam, so you can't get good uptake," says Dr. Hsu. "In earlier stages, treatment's a little more of a clinician judgment call, depending on whether they feel the patient is going to follow up regularly. Sometimes you can see people with some peripheral neovascularization but no vitreous hemorrhage and no symptoms. You don't have to treat those eyes according to the studies because they may still have good outcomes if you wait and only treat when high-risk characteristics develop."

There are well-known side effects to note with PRP, including decreased contrast sensitivity,[3] loss of visual acuity and constriction of the peripheral visual field.[4]

"One of the downsides of laser, which I discuss with patients, is that it may decrease peripheral vision and even night vision," says Dr. Hsu. "That's been well-demonstrated because you're essentially sacrificing the peripheral retina to save the central retina. But interestingly enough, I would say it's very rare for patients to actually complain after the laser that they lost peripheral vision because a lot of their peripheral retina is already pretty ischemic and not working too well to begin with. I'm also not doing super heavy PRP, like what may have been done decades ago before anti-VEGF was available. I still have some patients who had laser done 30 to 40 years ago who are doing great with 20/20 vision but the laser goes all the way to just outside the arcades. I assume that they have a much smaller field of vision, but they don't complain about it because they're still seeing well."



Ian C. Han, MD

Figure 3. These images are from a female patient in her 30s with poorly controlled type 1 diabetes. Due to social determinants of health (e.g., limited transportation), she had no prior eye care, and her right eye went blind due to neovascular glaucoma. She presented when the better-seeing left eye declined to count fingers visual acuity due to a subhyaloid hemorrhage and tractional retinal detachment with extensive, mature-appearing neovascularization of the disc and elsewhere (left). After prompt vitrectomy with membrane removal and laser placement, she recovered to 20/25 visual acuity (right), which she has maintained over years of subsequent follow up.

The other treatment option is anti-VEGF therapy. "Anti-VEGF blocks the major pathway that's leading to the neovascular growth we see in PDR and it's quite amazing," says Dr. Hsu. "For example, if you do an injection of an anti-VEGF agent and bring the patient back a few hours later or the next day, the vessels often just sort of melt away really quickly in response. It's also great that it's not destructive like PRP."

"When I started in ophthalmology, anti-VEGF was still fairly new in routine clinical practice, and we didn't expect patients to turn around on the one-way train of disease progression in PDR. All you were hoping for was to halt the progression of disease," says Dr. Han. "The initial indication for anti-VEGF therapy wasn't for PDR, but for diabetic macular edema. For example, the RISE and RIDE clinical trials with ranibizumab investigated the effect of anti-VEGF therapy in DME, but amazingly, it also reversed diabetic retinopathy severity for the majority of patients. Now, anti-VEGF therapy has a strong track record of working well and being effective, with the literature to support multiple anti-VEGF agents (bevacizumab [Avastin], ranibizumab [Lucentis], aflibercept [Eylea], etc.) with other newer drugs also now available (faricimab [Vabysmo])."

The CLARITY study, published in 2017, compared one-year best corrected visual acuity letter change from baseline results of PDR patients treated with the anti-VEGF aflibercept vs. PRP.[5] At 52 weeks, the outcome showed aflibercept was non-inferior and superior to PRP (mean best corrected visual acuity difference 3.9 letters [95% CI 2.3–5.6], $p<0.0001$). This backed up earlier findings of the Diabetic Retinopathy Clinical Research Network's Protocol S trial in 2015, which showed ranibizumab treatment resulted in visual acuity that was non-inferior to PRP when measured through two years.[6]

"That was a landmark study that really led to this paradigm shift of doing anti-VEGF over PRP because it shows equivalent outcomes with anti-VEGF therapy compared to PRP," says Dr. Hsu.

"In recent years, treatment for PDR has shifted toward injections, certainly if there's DME, and then you'll find a wide variety of practice patterns from PDR with no DME or

with just neovascular complications," says Dr. Han. "I think that has to do with what you think is the most effective treatment for the degree or severity of neovascularization that's out there. 'High-risk' PDR was defined decades ago (in the Diabetic Retinopathy Study) before anti-VEGF therapy or modern vitrectomy surgery. Nowadays, I think of a patient as being 'high-risk' based on social determinants of health that impact whether the patient can stick with a treatment regimen, or aspects of their disease that may cause irreversible vision loss such as traction leading to retinal detachment, or neovascular glaucoma."

The fact that anti-VEGF works so well can be to the patient's detriment, Dr. Hsu adds. "Sometimes it works so well that patients may think 'Oh, you cured me. I don't need to come back.' And they will see really well until the next bleed or something else happens," he says.

This is the crux of an ongoing debate among retina specialists. Both anti-VEGF and PRP require regular follow up, and considering anti-VEGF's lack of durability, some in the field argue it's not strong enough as a solo treatment.

"We see debates at meetings where there's a back and forth over which treatment is better, but I do agree the Holy Grail would be to come up with a non-destructive treatment," says Dr. Hsu. "Some have latched on to anti-VEGF as the non-destructive treatment, because the idea is that, as retina specialists, we want to preserve the functioning of the retina and not destroy it. And the concept of sacrificing the peripheral retina to save the central retina is not necessarily appealing to a lot of people.

"But I think on the flip side, we're just not there yet," Dr. Hsu continues. "The anti-VEGF era is here, but the delivery of it isn't ideal for these patients. Looking back at Protocol S, they went out to five years and they found that with the anti-VEGF injection, patients still needed on average three injections a year. So it's not like there's a long-term cure with continuous anti-VEGF therapy—as far as we know, they need to keep getting it indefinitely. If there was a one-and-done treatment that would provide a long-term anti-VEGF blockade, maybe that would be the Holy Grail and would be enough to move the needle away from laser in my mind. But personally, I think we're not there yet, because there's just too much at stake for these patients not to have PRP."

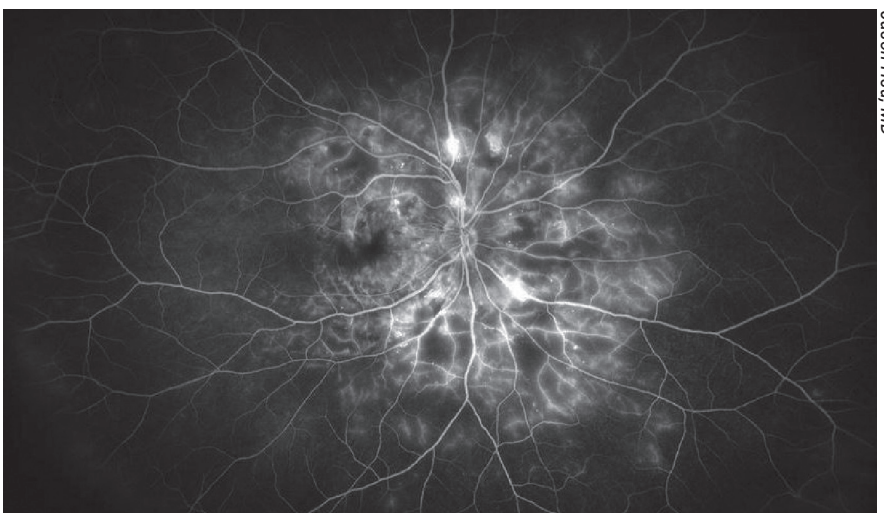
There's also some benefit to combining treatments. A 2022 collective review of studies assessing the impact of PRP and anti-VEGF for diabetic retinopathy found nine trials showing a combination therapy has a better impact on improving or delaying vision deterioration in BCVA, compared to monotherapy, as well as improving neovascularization regression with no potential increased incidence of adverse events.[8]

"My message for specialists who administer anti-VEGF injections is that it's critical to continue to perform PRP in eyes with PDR," says Dr. Hsu. "I realize that our practices are now built around injections, and it throws a wrench in the patient flow by throwing in a laser. PRP takes more time, but we shouldn't be sacrificing laser because it's inconvenient."

Before beginning any treatment, retina specialists have to ask themselves: How likely is it that this patient will follow through with treatment?

"Risk of loss to follow-up is huge," says Jennifer I. Lim, MD, the Marion H. Schenk Esq., chair in ophthalmology for research in the aging eye, a University of Illinois at Chicago distinguished professor of ophthalmology, the vice chair for diversity and inclusion, and director of the retina service at UIC. "If a patient is being given an anti-VEGF and they don't follow up, the downside is so much worse than if they were given PRP. If they have one anti-VEGF injection and they don't show up again, I have no idea: Did it work? Did it regress in a month, three months? And so those patients aren't the type I would want to put on an anti-VEGF."

She says some risk factors of losing patients to follow-up include being younger in age, working jobs where there aren't opportunities to take time off for appointments, if patients have to travel long distances for care, as well as their socioeconomic status and race.



Jason Hsu, MD

Figure 4. Wide-field fluorescein angiography image of the right eye of a patient with proliferative diabetic retinopathy demonstrating hyperfluorescent areas of vascular staining and leakage along with hypofluorescent areas of capillary nonperfusion.

Dr. Hsu studied just this[7] and identified three key risk factors of loss to follow-up (LTFU): type of procedure; age; and race. "LTFU is a bigger problem than we thought," he says. "Our research fellow, Anthony Obeid, and I first published the paper on this back in 2018. We were just looking at our own practice and focusing on high-risk patients with PDR who had either injections or PRP. The question we asked was, when a patient gets an anti-VEGF injection or PRP, how many of them don't come back for at least a year or more immediately after that treatment? We found that about a quarter of these patients in our practice were lost to follow-up and might not come back for a year or more—if ever.

"It's really eye-opening and scary," Dr. Hsu adds. "In our study, some of the risk factors for being lost to follow-up seemed to be younger age and being African American or Hispanic. We also conducted a zip code analysis of where the patients live and looked at the average adjusted gross income in that zip code in order to get an idea of income level. Patients who lived in areas with a lower AGI had a higher risk of loss to follow-up."

This then prompted another study that evaluated the outcomes of eyes that were LTFU for more than six months after their procedure. VA worsened significantly in both groups, 20/187 for anti-VEGF and 20/83 for PRP, but the PRP group returned to baseline after additional therapy, yet the anti-VEGF group didn't have as much improvement at 20/166.[9] The authors also discovered that 17 percent of eyes in the anti-VEGF group developed a tractional retinal detachment at the return visit, which increased to 30 percent by the final visit. In the PRP group, no eyes had a TRD at the return visit and only 2 percent had a TRD by the final visit.[9]

For this reason, some may even consider going with PRP in the first place. "With anti-VEGF, I never feel comfortable saying, 'Okay, I can see you back in a year,' " says Dr. Lim. "I've had patients who are very motivated to come in for their treatments, and even then they sometimes break in the middle, so lately I've been finding myself thinking it would be easier for the patient—and me in some ways—to just do the PRP because I think it's a more permanent solution. And you worry less about loss to follow-up, because there are some things out of the patient's control."

Dr. Hsu says there's no formula for predicting who will be lost to follow-up. "Many may think they can predict who will follow up by looking at certain patient characteristics," he says. "Unfortunately, we don't know when someone may lose their job or have an illness or some other issue and be unable to return. Still, we've got to encourage follow-up and keep track of these patients. It really is worthwhile to have someone on your staff tracking every patient who receives an injection or laser. If they're not coming back, bug them like crazy with phone calls, certified letters, whatever it takes. We're submitting a study soon showing our results after hiring a full-time person whose primary job is to do just that. While we found it made a difference, it still wasn't 100 percent."

Building Patient Trust

PDR treatment will be most successful when the physician-patient relationship is strong, say these doctors.

"Whenever I'm approaching treatment for PDR, I sit the patient down and very carefully explain to them what the consequences are if they don't show up," says Dr. Lim. "I develop a relationship similar to a team effort. Their job is to show up and report symptoms, and my job is to make sure that I treat them appropriately. I also encourage buy-in from them on what treatment we do, so it's a shared decision. Then patients feel like they've had a say in things and it wasn't being dictated to them."

Managing PDR for patients may also end up turning a patient's whole health in a positive direction, suggests Dr. Han. "With diabetic retinopathy, patients have seen a lot of medical providers in their lives already and heard a lot of bad news. Sometimes the thing that wakes them up is the seriousness of their eye condition, and it does take a lot to build trust. Treatment is about trust. This is a systemic disease, not just ocular, but you can save a life and turn the whole body—the whole patient—around. The eyes are often valued most and can be the motivation to get their life back in balance." ◀

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SUSTAINED DELIVERY AND GLAUCOMA: AN UPDATE

Multiple systems and devices are in the running to be safe and effective options.

CHRISTOPHER KENT
SENIOR EDITOR

Treating glaucoma with topical drops is problematic. Patient adherence is impossible to guarantee; drops can cause long-term damage to the corneal surface and/or meibomian glands;[1,2] and they can wash off the eye, thus requiring a significant amount of drug to be used. (One study found that corneal bioavailability of topical medication was less than 5 percent of the delivered amount.[3]) Sustained drug delivery could potentially bypass some or all of these problems.

Many different approaches to sustained delivery of glaucoma medications have been investigated. Noninvasive approaches have included drug-impregnated contact lenses, ocular rings that can be inserted under the upper and lower eyelids, collagen shields and drug-eluting punctal plugs. Invasive options have included subconjunctival injections of solutions and drug-eluting polymer microparticles, as well as drug-eluting implants like Allergan's Durysta, the only implant approved by the FDA at the time of this writing. (Intracameral implants seem to be particularly promising; in addition to Durysta, implants in the pipeline include Travoprost XR, a.k.a. ENV515 [Aerie/Alcon], the iDose TR travoprost implant [Glaukos], and the OTX-TIC travoprost intracameral implant [Ocular Therapeutix].) Other alternatives being investigated include supraciliary implants, microneedles and intravitreal nanosponges.

Overcoming Obstacles

Many of these sustained-drug-delivery systems have been shown to be effective, but practical problems have caused them to become stalled or abandoned. For example, drug-eluting punctal plugs have a number of potential problems to surmount. "In principle, drug-eluting punctal plugs are a good idea," says Malik Kahook, MD, the Slater Family Endowed Chair in Ophthalmology, chief of the Glaucoma Service and vice chair of translational research at the University of Colorado School of Medicine in Aurora, Colorado. "However, they often fall out post-insertion, and data have suggested that they may not deliver the drug consistently over a 90-day period."

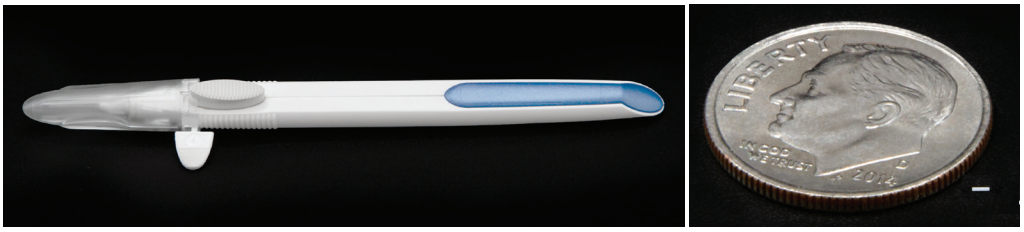
"A punctal plug is a foreign object with the potential to cause irritation, and rubbing can result in its dislodgement," notes Parul Ichhpujani, MD, a professor in the Department of Ophthalmology at the Government Medical College & Hospital in Chandigarh, India. "Movement of the plug can affect drug release, because the change in local milieu can cause it to malfunction. Sometimes the patient won't realize that the plug has dislodged, which would be detrimental to the IOP profile. Other potential problems include that, over a period of time, bacterial buildup may happen, so a preservative will be needed. How will the rate of drug release be titrated in such a scenario? And, there's no guarantee that the drug release and patient response will be uniform with subsequent plugs."

Nevertheless, work on this possibility continues. "In 2021, Mati Therapeutics purchased the rights related to the Evolute Punctal Plug Delivery System (PPDS) from

This article has no commercial sponsorship.

Dr. Medeiros has consulted for Allergan, Aerie, Novartis, Polyactiva and Ocular Therapeutix. **Dr. Kahook** receives patent royalties from New World Medical and Alcon and is the founder of SpyGlass Pharma. **Dr. Ichhpujani** reports no relevant financial ties.

Novelion Therapeutics," notes Dr. Ichhpujani. "Mati has completed multiple Phase II clinical trials using the Evolute platform in glaucoma and ocular hypertension patients. The punctal plug design has demonstrated good lower punctum retention rates of 92 percent and 96 percent in two separate multicenter U.S. clinical trials over a 12-week follow-up period."



Allergan's Durysta, currently FDA-approved for a single use, is now in Phase IV clinical trials to determine whether endothelial cell loss can be minimized with a longer interval between additional applications.

Surgical implants and injections have shown particular promise, but these alternatives also have issues to overcome. Because they're invasive, they're potentially associated with risks such as migration of the implant, endophthalmitis, endothelial cell loss and reactions to components of the devices. In addition, not every eye is eligible for such an implant. Finally, if problems arise, these options may not be easy to reverse.

"These approaches provide a few months of drug delivery," Dr. Kahook says. "However, they carry the risk of injuring the corneal endothelium. They're not anchored, so they can float around and mechanically injure tissue. Durysta, appears to work well, but it's only approved for one-time delivery because of the corneal risks."

Another option that seems to have stalled is sustained delivery via contact lens. Felipe A. Medeiros, MD, PhD, Distinguished Professor of Ophthalmology and vice chair for technology at Duke University in Durham, North Carolina, points out that one of the problems with this approach is that most glaucoma patients are older individuals. "These people are usually in their 60s or 70s, and they're not usually wearing contact lenses anymore," he says. "Contact lenses can be hard for some elderly patients to put on the eye. Also, contact lenses can cause serious complications, so you could be exchanging the side effects caused by topical drops for side effects caused by mishandling of the contact lenses, patients sleeping in their lenses, or contact lens-related infections. It's an interesting approach because it's noninvasive, but it hasn't really taken off."

Here, we'll review a few of the most promising sustained-release options under investigation, and provide an update on Durysta.

Allergan's Durysta

This implant, approved in 2020, is a rod-shaped, biodegradable polymer matrix containing 10 µm of bimatoprost that's released steadily inside the eye over a period of several months. It can be inserted into the iridocorneal angle in the clinic or operating room, where it dissolves gradually, eliminating the need for removal. Although it's only designed to last three to four months, studies have found that in some patients the treatment effect lasts far longer.[4-10] It has a favorable safety profile, with limited short-term adverse events that tend to be associated with the implantation procedure rather than the implant itself.

Two Phase III studies (ARTEMIS 1 and 2) have supported the safety and efficacy of the implant. Both studies randomized one eye of patients with ocular hypertension or POAG to an intracameral 10- or 15-µg bimatoprost implant, with the other eye receiving topical timolol 0.5% b.i.d. Multiple successive implants were permitted, as needed. Although significant implant biodegradation was observed in the majority of patients by 12 months, residual implants remained visible in the iridocorneal angle in more than 80 percent of the patients at month 20. (Corneal adverse events were more frequent with the larger 15-µg implant due to the volume of implant material in the iridocorneal angle after multiple implant administrations.) Some patients continued to have controlled IOP and stable visual fields more than three years after receiving their last implant.

"The Phase III studies involved three applications of the implant, spaced by four months," notes Dr. Medeiros, lead investigator in the clinical trials. "This was the original trial design, because in the early experimental work done in dogs, the drug would be gone by four months. In the Phase III trials we found that Durysta lowered the intraocular pressure very well, but in addition to that we were surprised to find that about 80 percent of the patients didn't need any rescue medication for up to one year after the third implant.

"A portion of the patients in the Phase III trial had significant endothelial cell loss," he continues. "However, this was mostly related to the presence of stacked implants in the anterior chamber. As a result, Durysta was approved for a single application, which may somewhat limit its clinical applicability."

"One-time delivery for a system that delivers drug for a few short months isn't ideal, given that glaucoma is a chronic disease requiring lifetime therapy," agrees Dr. Kahook. "However, even with limited approval it has a role in patients who need to buy time before having more definitive surgery, and in some other niche areas of treatment."

Dr. Medeiros points out that since the duration of effect is longer than four months for most patients, the interval between applications in the Phase III trials was likely too short. "In fact," he says, "our analysis of corneal endothelial cells after a single application doesn't show significant endothelial cell losses.[10] And, a recent study by Robert Weinreb, MD, et al showed that the implant is gone or has minimal size in about 80 percent of eyes after one year.[9]

"Right now, Phase IV studies are being done," he adds. "These studies are investigating optimal intervals between applications. With applications spaced out further, the likelihood of endothelial cell loss should be much lower. We hope this will lead to label expansion and approval for repeated applications."

The iDose Intracameral Implant

Glaukos' iDose is a 1.8 x 0.5 mm titanium implant designed to provide a steady release of travoprost into the anterior chamber over time. A scleral anchor holds the device in place in the trabecular meshwork. The targeted duration of therapy is six to 12 months. Unlike Durysta, the iDose implant is intended to be removed and replaced with a new device once the drug has been completely released.

A Phase II study found that at the primary 12-week endpoint, patients who had received a fast-eluting implant had a 33-percent decrease in IOP; patients who received a slow-eluting implant had a 32-percent decrease; and a control group receiving timolol twice a day had a 30-percent IOP decrease. The iDose IOP reduction was stable and sustained at 12 months after implantation. There were no serious adverse events.[11]

In September, Glaukos announced results from two Phase III clinical trials of the iDose. They reported that the system achieved its primary efficacy endpoints at three months in both trials, with high tolerability and a favorable safety profile. Specifically:

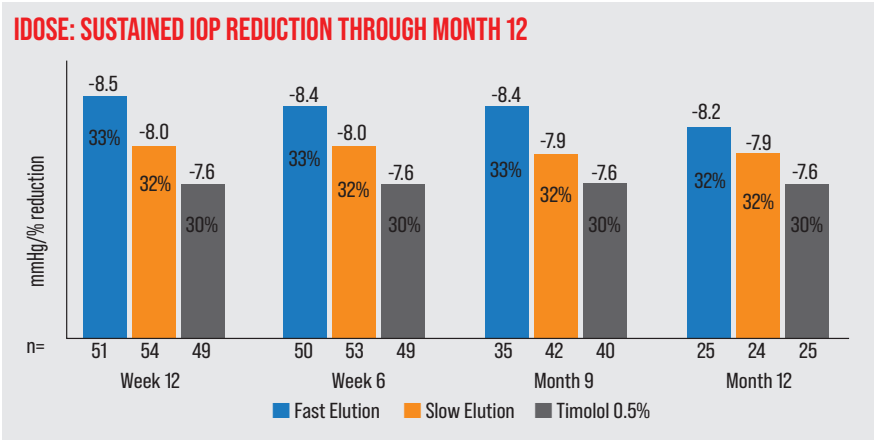
- Both the fast-release and slow-release devices were non-inferior to twice-daily topical timolol at three months.
- Ninety-three percent of slow-release iDose patients remained well-controlled on the same or fewer IOP-lowering topical medications at 12 months, compared to 67 percent of the timolol control subjects in both trials.
- Eighty-one percent of patients receiving the slow-release iDose were using no IOP-lowering topical medications at 12 months.
- In terms of tolerability, 98 percent of slow-release iDose subjects continued in the trial at 12 months, versus 95 percent of timolol control subjects.
- In terms of safety, the most frequent adverse event for slow-release iDose subjects was mild transient iritis, at a rate of 6 percent in both trials; the slow-release group also had a conjunctival hyperemia rate of 3 percent. No subjects experienced serious corneal adverse events, including endothelial cell loss, and no periorbital fat atrophy was observed.

"The good thing about iDose TR is that it's been designed to be removed and replaced with a new iDose TR when the effect wears off," says Dr. Ichhpujani. "Thus, it potentially offers a continuous, drop-free experience."

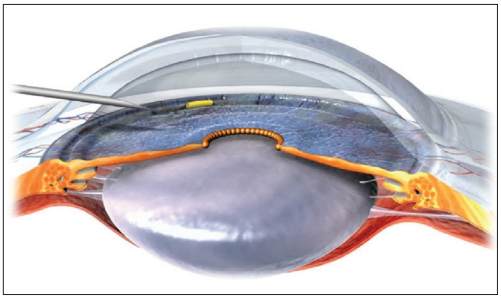
"iDose is the new kid on the block," notes Dr. Kahook. "The main advantage is that it can deliver the drug for a year or longer—and it seems to work in a manner similar to topical timolol. The possible cons are that you need to have the skill set to do intraoperative gonioscopy for trabecular meshwork implantation, and that the device is on the larger side, with the potential to injure both the cornea and iris if not implanted as indicated by Glaukos."

Dr. Medeiros agrees. "The iDose requires surgical insertion in the operating room," he says. "Although the device can provide sustained drug delivery for at least one year, it still needs to be replaced periodically, which may limit the patient population that would benefit from it. For example, patients who would be willing to have repeated surgical interventions over time would most likely be those with more advanced stages of glaucoma. However, those patients are usually already on multiple medications. That means that unless the device can be made to deliver multiple medications at the same time, these patients would still require eye drops.

"Also, this device is designed to be placed in the trabecular meshwork, which requires more skill than a simple injection into the anterior chamber," he adds. :There may also be a greater risk for complications, although we don't know that yet. We'll have to look at the data."



The iDose achieved 7.9-8.5 mmHg (32-33 percent) mean IOP reduction through month 12.



The OTX-TIC implant in the anterior chamber.

OTX-TIC Intracameral Implant

This device, from Ocular Therapeutix, is a proprietary, preservative-free, soft hydrogel platform embedded with travoprost-loaded microparticles that has a low potential for inflammation. According to the company, it has a meshwork that holds the microparticles; after being administered, the meshwork hydrates, allowing the microparticles to dissolve and diffuse the drug. It's placed into the iridocorneal angle using a 27- or 26-gauge needle, and it's fully biodegradable. The company says it remains visible during drug diffusion to allow monitoring, but is fully absorbed once the drug has been delivered. The system can be modified to deliver a variety of molecules of different sizes, and can be formulated to provide sustained release for days or months.

According to the company, early clinical trials of the travoprost implant have demonstrated that the system has an acceptable safety profile, maintains a steady level of the drug in the aqueous humor, and produces sustained IOP lowering.[12]

Travoprost XR

This biodegradable, rod-shaped intracameral implant, placed in the iridocorneal angle of the anterior chamber, uses nanoparticles to provide a steady supply of travoprost inside the eye for six to 12 months. Originally created by Envisia Therapeutics, the system is now being developed by Aerie/Alcon.

Several studies have confirmed its efficacy. A preclinical study using dogs demonstrated a 35.5-percent IOP reduction over an eight-month period.[13] A later Phase IIa study involving 21 glaucoma patients compared the implant to topical Travatan Z in the fellow eye. In this study, diurnal IOP dropped by 6.7 mmHg in the study group by day 25 (6.6 mmHg in the topical drop group), thus achieving its primary efficacy endpoint.[14] A third, 12-month study involved eyes of open-angle glaucoma patients previously treated with prostaglandins, using topical timolol once daily in the fellow eye for comparison. Mean IOP reduction at 11 months in the study eyes was 6.7 ±3.7 mmHg, or 25 percent—noninferior to timolol.[15]

Latanoprost FA SR

This biodegradable, rod-shaped intracameral implant, under development by PolyActiva (Parkville VIC, Australia) will deliver latanoprost. It's currently in Phase II studies.

IOL-haptic-based Drug Delivery

A new option under development is also worth noting. SpyGlass Pharma (Aliso Viejo, California) is developing a single-piece, hydrophobic acrylic IOL with two small drug-eluting pads that slide onto the haptics, attaching to the IOL at the haptic-optic junction. Once the pads are in place, the IOL and pads can be loaded into a standard IOL injector and placed into the capsular bag through a sub-2.4-mm incision using standard cataract surgical technique. The company explains that the pads remain outside of the visual axis and can continuously elute bimatoprost into the aqueous humor for three years. Preclinical testing in animals has found significant IOP lowering, no detectable systemic exposure and no drug-related adverse events, even with 10 times the standard dose.

An FIH feasibility study conducted outside the United States evaluated safety and efficacy in 23 patients with ocular hypertension or open-angle glaucoma. At three months, findings included:

- a 45-percent mean IOP reduction, regardless of dosage;
- 100 percent of patients were at 18 mmHg or less;
- all patients were off of topical drop therapy;
- no significant adverse events were reported;
- visual outcomes were similar to those achieved with commercially available IOLs.

The company plans to file an Investigational New Drug application within the next six months, and hopes to begin enrollment of patients in a Phase I/II clinical trial in 2023. Dr. Kahook, who founded the company, says that more clinical trial data will be forthcoming soon. "The pipeline for SpyGlass also includes no-drop cataract surgery options, as well as approaches designed to treat uveitis and macular degeneration," he says.

Looking Ahead

"It's imperative that we make sure these novel modalities can reach the masses, and not just be restricted to limited 'boutique' use," notes Dr. Ichhpujani. "They have to be safe, effective and easy to use, for a seamless integration into our individual practices. At the moment, there's not enough econometric evidence to

The SpyGlass system attaches drug-eluting pads to the haptics of an IOL. It may deliver a drug for three years.

EXTERNAL SUSTAINED-RELEASE DELIVERY OPTIONS OF NOTE

Two other options haven't appeared to move forward in the past few years, but may still be in the running:

• ***The Bimatoprost Ocular Ring.*** This device, from Allergan, is an extraocular polypropylene ring with an outer silicone matrix holding 13 mg of bimatoprost. The ring is inserted in the upper and lower fornices and is designed to elute the drug for about six months. A Phase II study involving 130 patients found that the ring produced clinically relevant reductions in IOP that were sustained across the six-month study period, although patients receiving topical timolol saw a greater reduction in IOP.[16]

Other findings from the study included:

— The ring was deemed to be safe and well-tolerated.

— The retention rate of the ocular insert was 93.1 percent at 12 weeks and 88.5 percent at six months. An open-label extension study found retention rates of 97.3 percent and 94.7 percent, suggesting that device retention increases with patient experience.[17]

— In the extension study more than 97 percent of participants found the ring to be tolerable, and more than 80 percent reported that it was comfortable.[17,18]

— Patients preferred the ring over eye drops.[14,15]

• ***The Topical Ophthalmic Drug Delivery Device.*** This device, also known as TODDD (Amorphex Therapeutics), is a soft polymer drug depot that steadily releases medication after being placed beneath the upper eye lid. Animal studies using 3 mg of timolol found a 37-percent reduction in IOP,[19,20] and an early study in 14 adult humans found a 70 percent retention rate after four weeks of continuous wear.[21] The manufacturer notes that the device allows easy and painless replacement in less than a minute, with no special tools required, and should cost less than an implant. The company is currently conducting studies using the device to deliver a prostaglandin; timolol; a prostaglandin plus timolol; and atropine. They anticipate the current set of studies will be completed by the end of 2024.

—CK

support their use in health-care systems funded by national health care insurance systems, or in countries with primarily out-of-pocket patient expenditure."

Asked what improvements she'd like to see in the future, Dr. Ichhpujani mentions two things. "Most novel drug delivery systems are focusing on delivering a single drug," she points out. "The next logical step would be to have a fixed-dose combination drug in a sustained device. Another desirable development would be a novel sustained delivery system coupled with an IOP-monitoring device, such as a drug-impregnated contact lens system."

"Out of all of the sustained delivery approaches under development, I think those that you inject into the anterior chamber have so far shown the best results in terms of convenience, pressure-lowering efficacy and safety," says Dr. Medeiros. "Many of the companies developing implants are focused on how the matrix holding the drug biodegrades over time, which is important; as noted earlier, the side effect of corneal endothelial cell loss seems to occur mainly as a result of residual implant material staying in the eye longer than would be desirable.

"I believe further developments in this area will lead to better implants and reduction in potential side effects," he concludes. "I think the field will be advancing quickly."

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Managing Glaucoma Patients' Low Vision

Don't underestimate the impact of decreased vision on your patients' lives.

SARWAT SALIM, MD, FACS
BOSTON

It's not uncommon for glaucoma patients to experience difficulty performing everyday tasks as a result of low vision, or visual acuity less than 20/40 in the better-seeing eye. They may struggle to see steps and changes in terrain, read menus or spot cars parked on the roadside at night. They're not alone. In fact, low vision affects approximately 7 million individuals in the United States, and the rates of low vision among the elderly are increasing. It's been estimated that the number of new cases of low vision and blindness each year will more than double in the next 30 years.[1]

Though glaucoma is the culprit behind a large share of these low-vision statistics, a review of literature highlights that it's not very common for glaucoma patients to use vision rehabilitation services. Here, I'll discuss why we should recommend these services to our patients, why vision rehabilitation is currently underutilized, how to perform low-vision evaluation, and which interventions are currently available to patients.

Why We Should Treat

Vision impairment has significant negative effects on patients' quality of life. Studies have reported that low vision may lead to a loss of independence, medication errors, increased risk of falling, social isolation, increased depressive and anxiety disorders, and increased mortality.[2-5] Patients with low vision most often complain of difficulty with reading, driving and mobility. Regarding the last, it's been reported that 49 percent of glaucoma patients struggle with steps, 42 percent with shopping and 36 percent with crossing roads.[6]

Even milder cases of glaucoma warrant attention for potential vision rehabilitation down the road. The Collaborative Initial Glaucoma Treatment Study reported that more than 25 percent of newly diagnosed glaucoma patients self-reported blurred vision and dark and light adaptation difficulties. Visual field testing showed only moderate correlation with these symptoms.[7]

Fortunately, vision rehabilitation can help improve patients' quality of life. Patient-reported outcomes indicate improvements in daily living and emotional well-being, such as reading ability, visual motor skills, mobility, safety, independence and overall quality of life.[8] Clinically

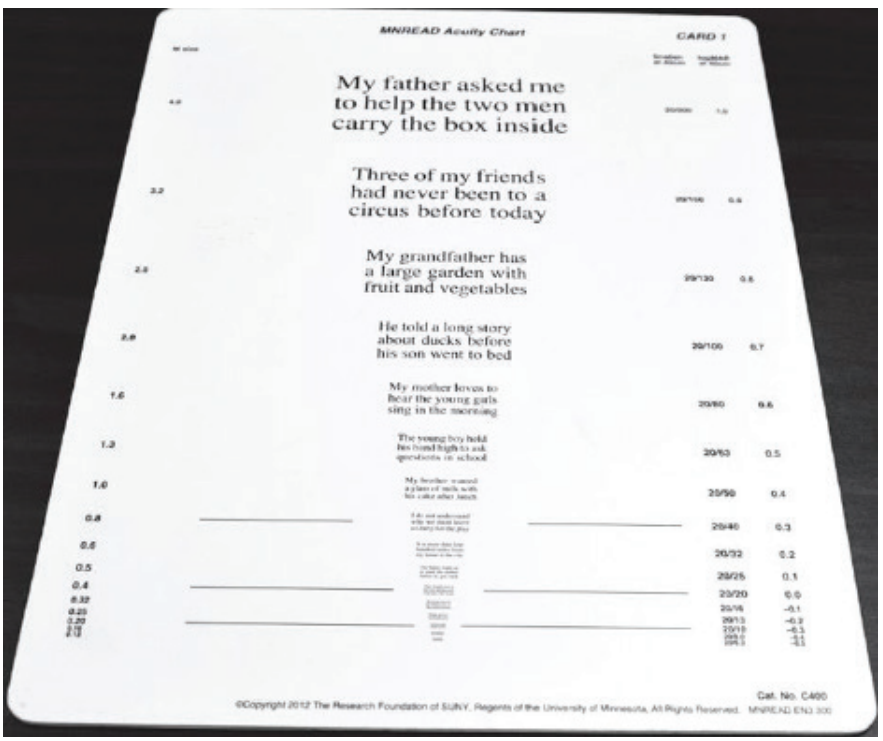

Figure 1. The Minnesota Low-Vision Reading (MNREAD) Chart can be used to determine the relationship of a scotoma to fixation in foveal-sparing scotoms.

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Dr. Singh is a professor of ophthalmology and chief of the Glaucoma Division at Stanford University School of Medicine. **Dr. Netland** is Vernah Scott Moyston Professor and Chair at the University of Virginia in Charlottesville.

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*Defined as modified Miyata grade 0, <25mv /mm^2 over 3 years (n=138), and over 9 years (n=20), respectively.

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Alcon

meaningful improvements in reading, emotional well-being and functional independence have also been reported three to six months after initiating certain therapies.[9] Clearly, it's worth referring glaucoma patients to vision rehabilitation early on to optimize their remaining vision and improve their overall quality of life.[10,11] One promising approach is computer-based vision rehabilitation training for glaucoma patients. This therapy has been shown to significantly increase patients' accuracy at detecting stimuli in high-resolution perimetry (p=0.007) and lead to faster reaction times (p=0.009) vs. visual discrimination placebo training.[12] The study reported that repetitively activating areas of residual vision and areas along the visual field borders resulted in increased detection sensitivity of stimuli and visual field defect improvements. The investigators proposed that neuroplasticity of the visual cortex or higher cortical areas may be the underlying mechanism of action.

Interestingly, a retrospective study on factors affecting recovery or restoration of neurological function reported that prolonged mental stress—which may be both a consequence and potential cause of neural inactivation—may influence outcomes.[13] The study authors hypothesized that stress-prone personalities traits (i.e., neuroticism, greater conscientiousness) would more likely suffer from vascular dysregulation and would therefore benefit most from alternating current stimulation (ACS) therapy, which improves blood flow. However, their correlations suggested that stress-prone personalities recovered less from ACS and those with physiological signs of vascular dysregulation recovered more. While the cause-and-effect relationship between stress and neurological recovery is still unclear, the paper suggested that psychosocial factors and vascular dysregulation likely contribute to the "highly variable" outcomes of patients in low-vision therapy. Personalized care and therapy plans may play a role in future visual and neurological rehabilitation efforts.

Accessing Rehabilitation

Despite the positive reported outcomes of vision rehabilitation, very few glaucoma patients use visual rehabilitation services. In fact, a 2009 study reported that only 14 percent of patients receiving these services had a glaucoma diagnosis and only 10 percent of patients with low vision are referred for vision rehabillitation.[14]

There are a number of reasons why patients don't receive visual rehabilitation. Barriers to care may include[15,16]

- lack of referral;
- ophthalmologists' lack of awareness of these services (an AGS membership survey reported that only 22 percent of survey-takers were high referrers with knowledge of published low-vision services guidelines);[17]
- lack of appreciation of the benefits available from these services;
- lack of time in clinics to provide counseling;
- lack of functional issues reported by patients;
- lack of transportation to services; and
- lack of financial resources to purchase low-vision devices.

For patients, many of these issues create a vicious cycle in which their functional issues make it increasingly difficult to secure transportation or funds to attend rehabilitation appointments. Therefore, their vision continues to deteriorate and they become further disadvantaged.

AAO Model of Vision Rehabilitation

A comprehensive vision rehabilitation plan may cover reading (the top reason patients seek vision rehabilitation),[18] daily living activities, safety and psychosocial well-being. The Academy's model of vision rehabili-

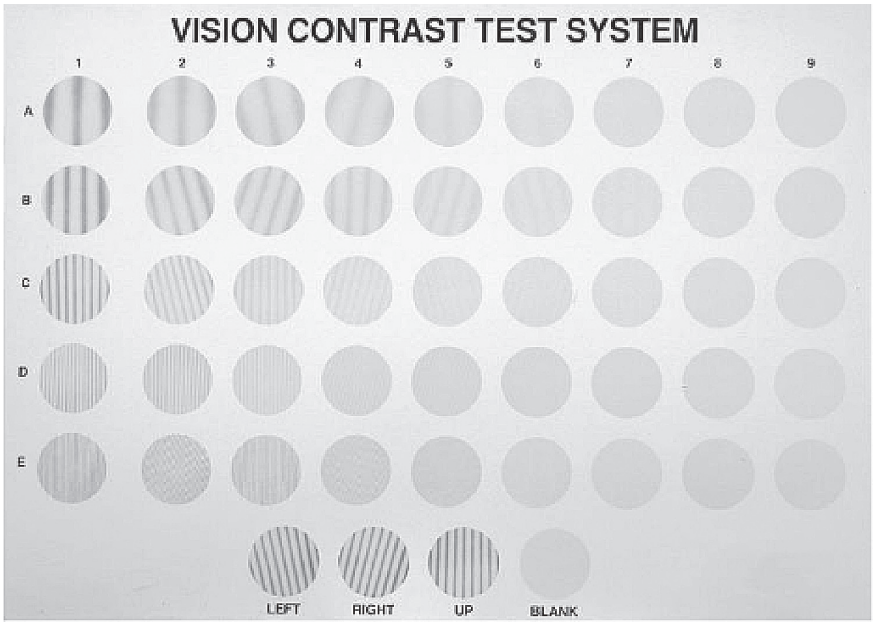

Figure 2. The Vistech contrast test uses sine-wave and bar patterns to assess vision worse than 20/40.

tation outlined in their Vision Rehabilitation Preferred Practice Pattern includes three levels:

• ***Level 1:*** Recognizing and responding to low vision. The first level depends on ophthalmologists recognizing patients with low vision and responding with education, counseling and/or referral to vision rehabilitation services.

• ***Level 2:*** Initiating clinician services. The second level includes services provided by a clinician specializing in vision rehabilitation.

• ***Level 3:*** Involving a multidisciplinary team. The third level's multidisciplinary team may include, but isn't limited to, clinicians, occupational therapists, social workers, psychologists, orientation and mobility trainers, community support groups, aging services, and transportation services.

Evaluating Patients

Visual acuity, visual fields and contrast sensitivity are the main components to evaluate when testing patients for low vision.

—Visual acuity testing. When testing visual acuity, it's important to test with high contrast charts and bright lighting. Commonly used projection charts aren't appropriate for this testing due to their low contrast and presentation in dark rooms. If using the ETDRS chart, bring it closer to the patient. The chart should be at a distance where at least the top line of letters can be seen by the patient.[19]

Watch the patient's head posture and eye movements as visual acuity is tested. A head turn may indicate that a patient has scotoma or is using an eccentric viewing location. Eccentric viewing is common among patients with central vision loss. Unlike foveal fixation, eccentric fixation occurs on the functioning peripheral retina, that is, the preferred retinal locus. Eccentric peripheral retinal loci are associated with lower visual acuity and less stable fixation, but this doesn't necessarily mean that patients with foveal fixation have better acuity. Foveal fixation may also be impaired and/or unstable. As patients shift fixation, measured visual acuity may vary. We can't assume that decreased visual acuity or unstable fixation means a patient is using eccentric peripheral retinal loci.[20]

Refracting patients with low vision is different than refracting those with normal visual potential. Retinoscopy and trial frames are good options. One may consider using full-aperture trial lenses since these allow the eccentric fixator to move the head or eyes as needed. Confirm the patient's refractive error after retinoscopy using fogging or cross-cylinder.[21]

—Visual field testing. When evaluating the patient's remaining visual field, pay attention to the location, size, shape, density and number of scotoma(s).

The Minnesota Low-Vision Reading (MNREAD) Chart is useful for determining the relationship of a scotoma to fixation in patients with a foveal-sparing scotoma (*Figure 1*). This text-based chart, available in multiple languages, assesses reading acuity (the smallest readable print); maximum reading speed (reading speed when performance isn't limited by print size); and critical print size (smallest readable print at maximum reading speed).[22] Print size decreases by 0.1 log unit steps, from 1.3 logMAR (Snellen equivalent 20/400 at 40 cm) to -0.5 logMAR (Snellen equivalent 20/6).

A patient with a scotoma to the right of fixation will find the next words in the chart obscured; with a scotoma to the left of fixation, one will have difficulty reading the beginning of the line. Scotomas above and/or below the peripheral retinal loci affect reading of the columns of numbers.

Another vision test for assessing scotomas called SKread is based on random word sequences. The unpredictable word and letter sequences make reading performance more dependent on eyesight rather than reading skill or educational level.[23]

—Contrast sensitivity testing. Contrast sensitivity is important for many daily tasks such as recognizing faces, objects, where steps begin and end, and for night driving. Two

tests that are useful for assessing contrast sensitivity are the Vistech contrast test (*Figure 2*), which uses sine-wave and bar patterns to assess vision worse than 20/40, and the Pelli-Robson contrast sensitivity chart (*Figure 3*), which uses letters of the same size but with decreasing contrast.

—Discussion of needs, limitations and goals. Be sure to talk to patients about their current limitations and needs, such as how their decreased vision affects their daily activities. Identifying low-vision patients and gauging their needs may be supplemented by administering the NEI VFQ-9 questionnaire, an abbreviated version of the NEI's 25-item Vision Function Questionnaire (NEI VFQ-25). Other questionnaires for screening patients for functional complaints, quality of life, and activities of daily living include the Activities of Daily Vision Scale (ADVS), Visual Function Index (VF-14), Visual Activities Questionnaire (VAQ) and Glaucoma Quality of Life (GQL-15).

Figure 3. The Pelli-Robson chart uses letters of the same size in decreasing contrast to evaluate contrast sensitivity.

Having conversations about realistic expectations is also important before embarking on a rehabilitation path. Though vision rehabilitation can improve many aspects of patients' lives, it isn't a magic bullet and doesn't restore their vision to pre-disease states. Focusing on management strategies to optimize remaining vision is key.

—Ocular/systemic disease evaluation. Evaluate any co-existing ocular diseases that patients may have. About two-thirds of patients with low vision have systemic diseases. Pay particular attention to diabetes, arthritis, and any neurological disorders such as tremors, paralysis or weakness.

—Inquire about visual hallucinations. Charles Bonnet Syndrome, which occurs in about a third of patients with some degree of vision loss, produces visual (but not auditory or other sensory) hallucinations.[24,25] Patients may see patterns, detailed images of people, places or events, or even imaginary creatures. CBS is attributed to a cortical release phenomenon resulting from lack of afferent visual information. In the absence of this visual data, the brain fills in the gaps with made-up images or recalls images from memory. These visual hallucinations usually stop after 12 months in about a quarter of patients. Managing strategies for coping with CBS, such as talking about the hallucinations with a trusted individual, resting, moving the eyes or looking away from the hallucination, or changing their environment can help the hallucinations to decrease or stop after a few years. Individuals with CBS are aware that what they're seeing isn't real.

Low-vision Interventions

There are numerous low-vision interventions available to patients. I recommend having examples of low-vision tools in the office to educate patients and normalize the devices and their use. Here are some tools to be aware of:

—Optical devices. Optical devices such as spectacles, magnifiers and telescopes are a good starting point for rehabilitation. High add-power glasses and high-plus reading glasses offer hands-free magnification and a large field of vision. These are best for short working distances and require good lighting. Readers with +4 D add are available over the counter. Readers greater than +4 D add require base in prisms to assist convergence and relax accommodation. Prism strength is 2 D more than the add.

To quickly estimate the needed add power, take the inverse of the patient's visual acuity (Kestenbaum Rule). For example, a patient with a 20/200 visual acuity would require 200/20 or 10 D of add. This rule doesn't factor in the effects of scotomas or decreased contrast sensitivity, however.

Handheld magnifiers can help patients perform short-term tasks such as browsing a menu. For longer tasks such as reading or near work, or for patients with tremors, stand magnifiers can help. Low-powered (+5 to +12 D) magnifiers are more commonly used due to comfort.

For higher magnification at a greater working distance than reading glasses, patients can opt for telemicroscopes, also called loupes. These are spectacle-mounted, binocular or monocular telescopes for near or distance tasks. They allow for a greater working distance than high-add reading glasses, but the visual field they offer is narrow, and depth of field is also reduced. These devices are useful for stationary distance viewing activities such as watching TV shows or sports. High

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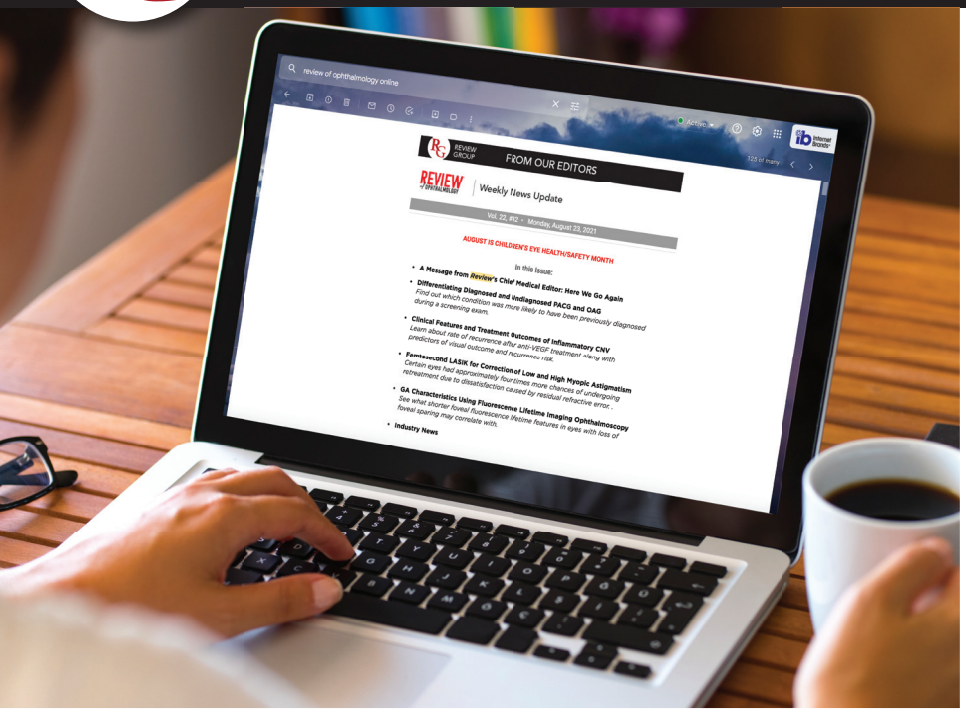

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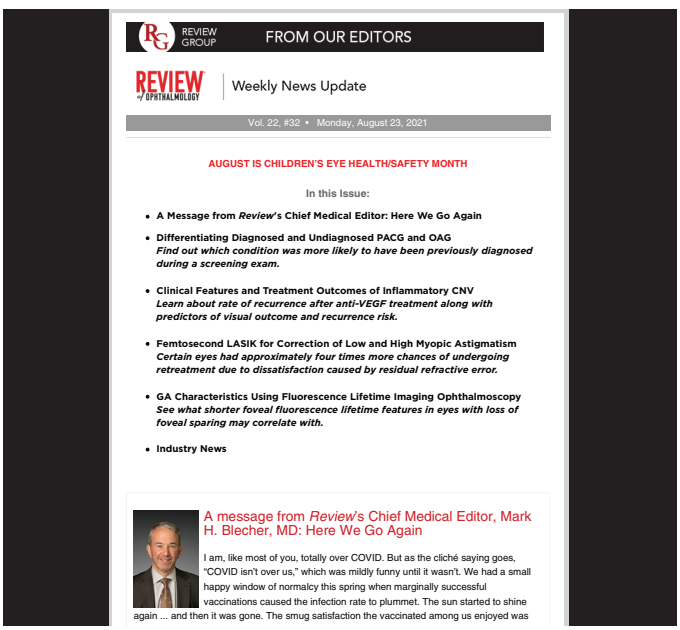
REVIEW GROUP FROM OUR EDITORS

REVIEW of OPHTHALMOLOGY | Weekly News Update

Vol. 22, #32 • Monday, August 23, 2021

AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

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A message from *Review*'s Chief Medical Editor, Mark H. Blecher, MD: Here We Go Again

I am, like most of you, totally over COVID. But as the cliché saying goes, "COVID isn't over us," which was mildly funny until it wasn't. We had a small happy window of normalcy this spring when marginally successful vaccinations caused the infection rate to plummet. The sun started to shine again ... and then it was gone. The smug satisfaction the vaccinated among us enjoyed was

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minus lenses and reverse telescopes may be used for patients with severe peripheral field loss who retain good central vision. These devices decrease image sizes (with an accompanying decrease in acuity). This enables more visual information to fit within the patient's small visual field.

Driving is an important issue to patients with vision problems related to glaucoma. Some states require special visual field testing (e.g., HVF 60-2) that patients may need to submit to their state division of motor vehicles. Also, states may allow bioptic driving, which allows for a small telescopic lens affixed to the standard lens on the better-seeing eye. A qualified driver with low vision may drive during daylight hours using a bioptic lens system. Availability of support for clinicians to gather required testing, complete forms, and services for fitting standard and low-vision optical devices are increasingly important in clinical care.

—Electronic devices. Smart magnifiers and video magnifiers, including computers, tablets, smartphones; and handheld, desk-mounted or head-mounted devices provide adjustable magnification and enhanced or reversed contrast without the peripheral distortion seen with glasses. Many feature text-to-speech conversion, using optical character recognition, or voice commands and voice outputs/screen readers. Many of these features can be activated in smartphones' accessibility settings. There are also several smartphone apps for visually impaired individuals. Electronic devices in general tend to be costly.

—Non-optical aids. Other options that can help individuals with low vision include direct task lighting such as gooseneck lamps or pocket flashlights; large-print or high-contrast reading material; sensory substitution such as tactile feedback (e.g., felt-tipped pens vs. ballpoint pens); and typoscopes, which are inexpensive cards that allow a patient to focus on one line of text at a time and help to filter out excess information and reduce glare.

Environmental modifications may also be employed. Tripping hazards in the home can be reduced by marking steps or certain objects with high-contrast tape. Occupational therapy can assist patients with head- and eye-scanning strategies to increase environmental awareness and mobility. Some patients may opt for using a white cane to aid obstacle detection or signal to others that they're visually impaired.

With so many options and often limited clinic time, it's a good idea to have a handout to give to patients explaining low vision, rehabilitation and intervention options. The Academy's handout on low vision for patients can be found at aao.org/low-vision-and-vision-rehab (scroll to "Materials for Patients with Low Vision"). This page also contains a link to the Vision Rehabilitation Preferred Practice Pattern guidelines.

Glaucoma is a difficult disease to manage, and the visual changes that accompany it are often frightening and distressing for patients. We must be aware of how this disease impacts patients' functional daily living and be ready to recommend vision rehabilitation. Low vision management in glaucoma requires a multidisciplinary effort but the results can make a major difference for patients. ◂

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ABOUT THE AUTHOR

Dr. Salim is a professor of ophthalmology, the vice chair for clinical and academic affairs and the director of the glaucoma service at The New England Eye Center at Tufts University School of Medicine. She has no related financial disclosures.

An Update on the Anti-VEGF Biosimilar Pipeline

Biosimilars for diseases like AMD and diabetic retinopathy could possibly offer patients effective, less-costly options.

JENNIFER I. LIM MD, FARVO, FASRS
CHICAGO

Imitation is the sincerest form of flattery. It also may be the sincerest way to make effective medications more affordable for patients with retinal conditions in the form of biosimilars, which can offer similar efficacy as their reference products at about 40 percent of the price. Two biosimilars for ophthalmic indications have been approved in the United States already and more appear to be on the way. Here, we'll take a look at the development of biosimilars in retina and the safety and efficacy of agents both approved and in development.

Biosimilar Background

In the United States, intravitreal anti-VEGF agents approved by the Food and Drug Administration include not only ranibizumab, aflibercept, brolucizumab and faricimab, but also recently approved biosimilar anti-VEGF agents. All of these anti-VEGFs are biotechnology-derived protein products, classified as biologics.[1] As such, their production entails the use of living cells with culture media and various excipients that result in slight differences between lots; these differences are accepted as normal and expected. The FDA assesses the manufacturing process and the manufacturer's strategies to control and monitor these within-product variations in order to produce a biologic with consistent clinical performance. The patented and FDA-approved biological product is termed an FDA "reference product," and serves as the standard to which biosimilars are compared. Examples of reference products include ranibizumab, aflibercept and bevacizumab. The expiration of the patents for ranibizumab and bevacizumab in the United States (2020 and 2019, respectively) facilitated the development of less costly biosimilars.[2]

Cimerli was deemed interchangeable with ranibizumab.

A biosimilar is a biologic product that's very similar to the reference product, with no clinically meaningful difference in terms of safety, purity or potency.[3] Guidelines for the approval of biosimilars were first created in Europe, where the European Medicines Agency created an abbreviated registration process in 2005-2006, resulting in the EMA's first approved biosimilar, a somatropin biosimilar called Omnitrope, in 2006.[2] In the United States, The U.S. Patient Protection and Affordable Care Act created an abbreviated licensure pathway for biosimilars (351(k) pathway) under the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which was signed into law in 2010. The final guidance on implementation of the 351(k) pathway was in 2015.[4] The FDA approved its first biosimilar in 2015.

The driving force for creation of biosimilars is the lower cost, which can lead to improved affordability and accessibility to the anti-VEGFs. Biosimilars cost less than the reference product because research and development costs are cheaper. This is primarily due to lower clinical trial costs since the FDA requires much less extensive clinical trials for biosimilar approval compared to approval of a reference product. Indeed, current biosimilars cost about 40 percent less than the reference product.[2]

Approving a Biosimilar

The FDA approval process for a biosimilar differs from that of the reference product. In contrast to the reference product, which must demonstrate efficacy and safety in costly clinical trials, a biosimilar just needs to show it's similar to the refer-

This article has no commercial sponsorship.

Dr. Regillo is the director of the Retina Service of Wills Eye Hospital, a professor of ophthalmology at Thomas Jefferson University School of Medicine and the principle investigator for numerous major international clinical trials.
Dr. Yonekawa is an assistant professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University. He serves on the Education Committee of the American Society of Retina Specialists and on the Executive Committee for the Vit Buckle Society, where he is also the vice president for academic programming.

ence product and that its treatment outcomes wouldn't be expected to differ from the reference product. The manufacturer must show that high similarity to the reference product's biological activity, purity and structure. The primary endpoint is selected as a sensitivity endpoint, which shows the highest change from baseline for the treatment response. For anti-VEGFs, the most rapid change in visual acuity occurs within the first eight to 12 weeks of initiating therapy. Thus, the non-inferiority studies for anti-VEGF biosimilars use a primary endpoint of change in mean visual acuity from baseline at eight to 12 weeks.

Unlike non-biologically derived drugs for which generic drugs copy an identical chemical formula, biologics are produced by living cells and there isn't a chemical formula or recipe for production. Differences in clinically inactive components are acceptable; these include differences in stabilizers and buffers. Safety is demonstrated through human pharmacokinetic (exposure) and efficacy through pharmacodynamic (response) studies. In addition, an assessment of clinical immunogenicity as compared to the reference drug is also needed as antidrug antibodies (ADA) develop in response to intravitreal injection of anti-VEGFs into the vitreous.[5]

In the approval process for a biosimilar, extrapolation to disease indications that weren't studied in a clinical trial may be granted if FDA review of the data shows no differences between the biosimilar and the reference product. The FDA works with the manufacturer to determine what data are needed for extrapolation.[6] Designation of "interchangeable" may also be granted by the FDA if the data shows the biosimilar would be expected to result in the same clinical result as the reference product. Usually this includes studies in which repeated doses are given and for which safety and effectiveness are shown when switching back and forth between the reference and the biosimilar product. It's important to be aware that an interchangeable biosimilar can be substituted for the reference product by a pharmacy without the physician being aware of this substitution. These laws pertaining to pharmacy-level substitution vary from state to state.

RETINA BIOSIMILARS APPROVED OR IN DEVELOPMENT

FDA-approved	
Name	**Company**
Byooviz (ranibizumab biosimilar)	Samsung/Bioepis
Cimerli (ranibizumab biosimilar)	Coherus
In-development	
Name	**Company/country**
Ranibizumab biosimilars	
Xlucane	Xbrane, Sweden; Phase III
R-TPR-024	Reliance Life Sciences, India; Phase III
SJP-0133	Senju Pharmaceuticals, Japan: Phase III
LUBT010	Lupin, India; Phase III
CKD-701	Chong Kun Dang Pharmaceutical, South Korea; Phase III
Aflibercept biosimilars	
SB15	Samsung Bioepis
MYL1701	Momenta Pharma and Viatris
ABP-938	Amgen, United States
FYB203	Formyon AG/Bioeq, Germany; Phase III nAMD
SOK583A19	Sandoz, Switzerland; Phase III nAMD
CT-P42	Celltrion, South Korea;Phase III DME
ALT-L9	Alteogen, South Korea; Phase I AMD
OT-702	Ocumension Therapeutics/Shandong Boan Biological Technology, China; Phase III
Bevacizumab biosimilar	
Bevacizumab-vikg (Lytenava)	ONS-5010, Outlook Therapeutics, Phase III

Biosimilars' Reception

Introduction of biosimilars into medicine has been met with some initial resistance. Uptake of the use of biosimilars is typically slow initially and then accelerates as providers become more educated about them.[7] A contributing factor to this slow uptake is known as the "nocebo" effect, which is defined as the "incitement or the worsening of symptoms induced by any negative attitude from non-pharmacological therapeutic intervention, sham or active therapies."[8] In order to combat this factor, there needs to be effective, clear, data-driven communication of the biosimilar by the physician to the patient. Positive framing, data about similarity and expected outcomes, and a unified office approach to the biosimilar should help decrease the nocebo effect.

The FDA has implemented initiatives to improve access to biosimilars in the United States. The agency's Biosimilars Action Plan (July 2018) was created to improve the efficiency of development and approval of biosimilars, including supporting education and communication to improve understanding of the drugs.[3] In other areas of medicine, such as oncology, biosimilars are commonplace.

In the following sections, we'll discuss the biosimilars in the retina space.

Ranibizumab Biosimilars

There are several ranibizumab biosimilars, some of which are approved in the United States: Byooviz (SB11) and Cimerli (FYB 201). Other biosimilars in development include Xlucane (Sweden), R-TPR-024 (India), SJP-0133 (Japan), LUBT010 (India) and CKD-701 (South Korea).[9]

In 2015, India became the first country to launch a biosimilar of ranibizumab, known as Razumab, (Intas Pharmaceuticals; Ahmedabad, Gujarat, India) for the treatment of neovascular AMD, diabetic macular edema and retinal vein occlusion.[10-15] The Phase III clinical trial was for the treatment of AMD. Subsequent retrospective studies included RE-ENACT[12-14] and CESAR (Clinical Efficacy and Safety of Razumab).[15] The introduction of this biosimilar was associated with inflammatory reactions, specifically sterile endophthalmitis, from the use of specific batches of Razumab.[16] These were found to be due to higher endotoxin levels in the buffer used for manufacturing. Since then, an extensive review has demonstrated good results for Razumab in India.[17]

The first FDA-approved biosimilar was for ranibizumab. Ranibizumab-nuna (SB11, Byooviz; Biogen/Samsung Bioepis, South Korea) was approved in September 2021 for treatment of nAMD, macular edema from RVO and myopic choroidal neovascularization. In the Phase III non-inferiority clinical trial of SB11 in nAMD, 705 patients were randomized (1:1) to receive SB11 or reference ranibizumab monthly injections (0.5 mg) in an equivalence study with a primary equivalence endpoint was at week eight and follow-up through week 24.[18] Equivalence was demonstrated for safety, efficacy and immunogenicity. Extended follow-up at week 52 for 634 patients who continued to receive treatment up to week 48 continued to show equivalence for efficacy and safety. The Least Squares (LS) mean change in best-corrected visual acuity from baseline at week 52 was 9.79 letters for SB11, compared with 10.41 letters for reference ranibizumab (difference: -0.62, [90% CI: -2.092, 0.857]). The LS mean change in central subfield thickness (CST) was –139.55 µm for SB11 vs –124.46 µm for reference ranibizumab (difference: -15.09, [95% CI, -25.617, -4.563]). At all timepoints studied up to week 52, pharmacokinetic, safety and immunogenicity profiles of SB11 were comparable to reference ranibizumab.[19]

In October 2022, FYB-201, ranibizumab-eqrn (Cimerli, Coherus BioSciences) became FDA approved as the only interchangeable biosimilar to the reference ranibizumab (Lucentis, Genentech) for all ranibizumab indications. It's available in both 0.3-mg and 0.5-mg dosages for nAMD, macular edema following RVO, DME, diabetic retinopathy and mCNV.[20] The interchangeability designation resulted from the FDA assessment that ranibizumab-eqrn met FDA safety, efficacy and quality standards to the reference product. This included comprehensive studies involving analytical, preclinical and clinical programs to confirm equivalent safety and efficacy to ranibizumab. Cimerli was granted 12 months of interchangeability exclusivity.

Byooviz was the first biosimilar FDA approved for macular degeneration.

In the Phase III COLUMBUS-AMD study, 477 patients were randomized to receive monthly ranibizumab-eqrn 0.5 mg or reference ranibizumab 0.5 mg in a non-inferiority design.[21] The primary endpoint was change in best-corrected visual acuity after eight weeks, with an equivalence margin of three letters. Ranibizumab-eqrn met the primary endpoint with an improvement of 5.1 letters as compared with reference ranibizumab showing an improvement of 5.6 letters (-0.4 difference, 90% CI -1.6 to 0.9). Ocular and systemic safety profiles were similar between the treatment groups. Secondary endpoints included mean change in BCVA from baseline, change from baseline in retinal thickness at 48 weeks, safety and immunogenicity. The overall safety and immunogenicity profile was comparable to ranibizumab's. Based on the totality of evidence, ranibizumab-eqrn demonstrated that clinical outcomes are expected to be the same for any given patient across all indications.

Aflibercept Biosimilars

SB15 (Samsung Bioepis) and MYL1701 (Momenta Pharmaceuticals and Viatris) are two aflibercept biosimilars in development that currently have some clinical trial results available. Other aflibercept biosimilars being developed include:

- ABP-938 (Amgen, U.S.);
- FYB203 (Formycon AG/ Bioeq, Germany; Phase III nAMD MAGELLAN study);
- SOK583A19 (Sandoz, Switzerland; Phase III nAMD MYLIGHT study)
- CT-P42 (Celltrion, South Korea; Phase III DME);
- ALT-L9 (Alteogen, South Korea; Phase I nAMD);
- OT-702 (Ocumension Therapeutics/Shandong Boan Biological Technology, China; Phase III).[9]

SB15 is being studied in a Phase III clinical trial in treatment-naïve

nAMD patients. Patients were randomized to receive either SB15 or reference product aflibercept. At week 32, patients in the reference aflibercept group are randomized to continue receiving reference product or switched to the biosimilar. The primary endpoint, change in BCVA from baseline at week eight, was achieved with 6.7 letters for SB15 and 6.6 letters for aflibercept, (95% confidence interval [CI], -1.3 to 1.4). Equivalent changes in BCVA and OCT CST were seen up to week 32. No new safety signals were found, and the AEs were similar in incidence and severity between SB15 and reference aflibercept up to week 32. Immunogenicity and pharmacokinetic profiles were also similar.[22] The final results at week 52 will soon be available.

MYL-1701P is an aflibercept biosimilar candidate being evaluated in the Phase III clinical trial INSIGHT in DME patients. In that study, 355 patients were randomized to receive either MYL-1701P or the reference product aflibercept. At week eight, the primary endpoint, mean change in BCVA, showed therapeutic equivalence between the drugs. Secondary endpoints included analysis of proportion of patients who gained ≥15 ETDRS letters from baseline and safety outcomes. Similar proportions of patients gained > 5 letters at eight weeks (61.4 percent biosimilar versus 62.8 percent reference aflibercept) and similar rates of ≥10 and ≥15 letters improvement were seen. Safety was demonstrated and no significant differences in antidrug antibodies were seen. Follow up was up to 52 weeks.[23]

Bevacizumab Biosimilars

There are three bevacizumab approved biosimilars in the United States, all for intravenous oncologic applications.[24] It's important to note that they're not approved for intraocular use, and it's not recommended to use them intraocularly. The drugs are bevacizumab-awwb, ABP215 (Mvasi), approved in September 2017; bevacizumab-bvzr (PF-06439535, Zirabev), approved in Jun 2019; and bevacizumab-maly (Almysys), approved in April 2022.

In contrast, bevacizumab-vikg (ONS-5010/Lytenava, Outlook Therapeutics) was developed for intraocular use and is being evaluated for that indication. Three registration trials have been performed for ONS-5010 and several more are in the works. In NORSE ONE, 61 nAMD patients received ONS-5010 or ranibizumab 0.5 mg. Positive efficacy and safety in the first trial led to NORSE TWO, the pivotal Phase III superiority trial for nAMD. In NORSE TWO, 228 patients were randomized to bevacizumab-bvzr mg dosed monthly or ranibizumab 0.5 mg dosed monthly for three months, and then quarterly (PIER dosing regimen) up to month 12. The primary endpoint, the difference in the proportion of patients who gained at least 15 letters in BCVA at 11 months, was reached in 41.7 percent (p=0.0052). NORSE THREE is an open label study that enrolled 197 patients and showed a positive safety profile. NORSE FOUR is planned for BRVO and NORSE FIVE and SIX are planned for DME.[25]

ONS-5010 has been filed as a new biologic with the FDA instead of as a biosimilar because there's no FDA approved bevacizumab for ophthalmic indications.

In conclusion, biosimilars offer affordability and accessibility to anti-VEGF therapy as compared to reference anti-VEGFs. This premise requires that ophthalmologists embrace the use of biosimilars. Only time will tell if ophthalmologists indeed choose biosimilars as first-line agents, because of their lower cost and results that are expected to be similar to reference anti-VEGF products. Although the data indeed show equivalence in terms of efficacy and safety, data are only available for up to one year for the approved biosimilars in the United States. More experience with biosimilars will show whether these agents can continue to show safety profiles similar to those of reference anti-VEGFs over the long term. Eventually, with continued demonstration of safety in real-world studies, it's likely that physicians will become more comfortable with these biosimilars, and their use will increase. In the future, however, the introduction of newer agents that have greater efficacy and durability will compete with biosimilars and existing anti-VEGFs. Until then, biosimilars offer us another option for treating our patients.◀

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ABOUT THE AUTHOR

Dr. Lim is the Marion H. Schenk Esq., Chair and UIC Distinguished Professor of Ophthalmology and director of the Retina Service at the University of Illinois at Chicago.

MARY PAT JOHNSON, COMT, CPC, COE, CPMA

MEDICARE Q&A

The 2023 Coding and Reimbursement Update

Every year, the government tweaks the rules for reimbursement. Here's what you need to know.

The start of the new year is a perfect time to review updates in place for 2023 and perhaps revisit your compliance efforts to help ensure continued accuracy in your billing procedures. This article highlights important changes for coding, reimbursement and regulations that impact ophthalmic practices.

Q What's new in terms of provider reimbursement?

A The 2023 Medicare Physician Fee Schedule (MPFS) was published in the Federal Register on November 1, 2022. MACRA provided a neutral (0.0 percent) update to physician payments for 2023. However, when you factor in required budget neutrality adjustments and the expiration of the 3-percent increase to the 2022 PFS payments, the proposed 2023 PFS conversion factor, is $33.06; a decrease of 4.6 percent. Then include the 2 percent sequestration payment adjustment applied to all Medicare Fee-for-Service claims and the PAYGO cuts. The result is a 10.6-percent cut to Medicare rates in 2023.

Due to changes in RVUs for certain services, not all codes are impacted equally. Below, we'll look at a few of the more notable changes (percentage change amounts appear in Table 1).

Q What's new for facility reimbursements?

A ASCs that met their quality reporting requirements received a 3.8-percent increase to the conversion factor, now $15.813.[2]

Those that failed to meet their quality requirements in the most recent reporting year saw only a 1.8-percent increase.

Payment rates for hospital outpatient departments (HOPDs) also went up 3.8 percent. Table 2 lists the 2022 and 2023 Medicare ASC and HOPD allowed amounts for a few common ophthalmic procedures.

The CPT codes for procedures with an artificial iris (0616T, 0617T and 0618T) have all been assigned to a single APC (APC5495) due to the offset percentage for the prosthetic device. When the device offset percentage exceeds 30 percent, CMS assigns higher rates to the ASC.[3]

For 2023, Quality measures ASC-1 through ASC-4 are required, and providers are now required to submit quality-measures data, rather than claims, through the HQR System (formerly known as the QualityNet

TABLE 1. REIMBURSEMENT CHANGES FOR 2023

CPT	Short Descriptor	2022	2023	Change	Percentage Change
92235	Fluorescein angiography	$126	$135	$9	7.14%
67311	Revise eye muscle, horizontal	$484	$443	-$41	-8.47%
92136	Optical coherence biometry	$51	$46	-$5	-9.80%
67350	Optic nerve decompression	$1,418	$1,253	-$165	-11.64%
67314	Revise eye muscle, vertical	$554	$443	-$111	-20.04%
66174	Canaloplasty	$761	$607	-$154	-20.24%
92284	Dark adaptation exam	$59	$46	-$13	-22.03%
67332	Revise eye muscle(s) add on	$263	$204	-$59	-22.43%
67334	Revise eye muscle with suture	$239	$185	-$54	-22.59%
67320	Revise eye muscle(s) add on	$256	$198	-$58	-22.66%
92287	AS imaging with F	$184	$142	-$42	-22.83%
92060	Orthoptic training, by physician or QHP	$54	$40	-$14	-25.93%

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Mary Pat Johnson is a senior consultant at the Corcoran Consulting Group and is based in North Carolina. She can be reached at mpjohnson@corcoranccg.com.

Secure Portal). Because reporting will no longer be claims-based, measures are required on all patients, not just Medicare ones.[4]

Q What are the latest rules for reimbursement for injectables in an ASC?

A ASCs will continue to receive separate reimbursement for Omidria (J1097) under Medicare regulations.

The pass-through status for Dextenza (J1096) and Dexycu (J1095) expired on 12/31/22. Under Medicare regulations for non-opioid pain management drugs and supplies, Dextenza will continue to be reimbursed separately in the ASC. It won't be paid separately in an HOPD.

Insertion of the Dextenza implant is identified with code 68841 (Insertion of drug-eluting implant, including punctal dilation, when performed, into lacrimal caliculus each) which was reassigned to APC5503. The ASC won't receive reimbursement for 66841 when it's performed with concurrent procedures. The ASC may be paid for the insertion when it's done as a standalone procedure.

ASCs will no longer be paid separately for Dexycu (J1095), since it doesn't qualify as a non-opioid pain management drug.

Q What changes have been made to CPT codes?

A Coding for evaluation and management (E/M) services again took center stage in 2023 as the AMA revised the inpatient E/M codes to correlate with the guidelines for office and outpatient coding. No longer will the elements of the documented patient history or physician exam impact the level of service. Select the level of service for these E/M codes based solely on the medical decision making or the physician time dedicated to the encounter. The changes apply to hospitals, nursing homes and a patients' residences, as detailed below.

In a hospital setting, the following codes were revised:

- initial hospital inpatient or observation care (CPT codes 99221 – 99223) (note the codes for initial observation care [note that CPT codes 99224 -99226] have been deleted);
- subsequent hospital inpatient or observation care (CPT codes 99221 – 99233) (note CPT codes 99218 – 99220 have been deleted);
- hospital inpatient or observation care services (including admission and discharge, CPT codes 99234 – 99236);
- hospital inpatient discharge services (CPT codes 99238 and 99239) (note CPT 99217 has been deleted); and
- emergency department services (CPT codes 99281 – 99285).

In terms of CPT coding, the "nursing facility" includes skilled nursing facilities, psychiatric residential treatment centers and immediate care facilities.

In those settings, the following codes were revised:

- initial nursing facility care (CPT 99304 – 99306);
- subsequent nursing facility care (CPT 99307 – 99310) (note that code 99218 has been deleted this year);
- nursing facility discharge services (CPT 99315 and 99316);
- domiciliary, rest home or custodial care services, new patient (CPT 99341 – 99345) (note that codes 99324 – 99324 have been deleted); and
- domiciliary, rest home or custodial care services, established patient (CPT 99347 – 99350) (note that codes 99334 – 99347 have been deleted).

The 2021 Evaluation and Management guidelines now apply to both outpatient (CPT 99241 – 99245) and inpatient (CPT 99251 – 99255) consultations. Medicare hasn't reimbursed for consultations for several years, but some other payers do.

Q What are the changes to prolonged-service codes?

A When coding is based on physician time spent, remember that extraordinarily long encounters that exceed the physician requirements for the assigned E/M code can be reported with an additional code. AMA provides code 99417 for prolonged encounters with the patient and code 99349 for prolonged services without a same day patient encounter. Report the prolonged service once for each 15-minute increment.

For Medicare claims, there are three same-day prolonged-service codes, each based on the place of service:

- G0316–Prolonged E/M, hospital inpatient, each additional 15 min;
- G0317–Prolonged E/M, nursing facility, each additional 15 min; and
- G0318–Prolonged E/M, home or residence, each additional 15 min.

Selecting the specific code level based on medical decision making or physician time dedicated to each of these codes is beyond the scope of this article. Physicians and coders are encouraged to review the updated information in the 2023 CPT manual.

Other than these E/M code updates, CPT has only a few new codes, revisions and deletions applicable to ophthalmology. The affected codes are listed below. For the revised codes, the text shown here as underlined is new to the code definition.

Revised codes:

- 66714–Transluminal dilation of aqueous outflow canal (e.g., canaloplasty); without retention of device or stent;
  - — 66174–with retention of device or stent;
- 92065–Orthoptic training; performed by a physician or QHP (don't report 92065 in conjunction with 92066, 0687T, 0688T, when

performed on the same day);
• 92229–Imaging of retina for detection or monitoring of disease, point of care autonomous analysis and report; unilateral or bilateral; and
• 92284–Diagnostic dark adaptation examination with interpretation and report.

These are the new CPT codes for 2023:
• 0730T–Trabeculotomy by laser, including optical coherence tomography guidance (Effective: July 1, 2022, Sunset January 2028); and
• 92066–Orthoptic training; performed under supervision of a physician or QHP (don't report 92065 in conjunction with 92066, 0687T, 0688T, when performed on the same day).

Q What ICD-10 changes should I be aware of?

A ICD-10 code changes and updates apply on October 1st each year so the update for 2023 is already in effect. There were 1,492 new, revised or deleted codes, but none that impact ophthalmology. There are instructions clarifying how to code the use of insulin when used with a non-insulin medication or when used on a temporary basis. They are as follows:
• for oral hypoglycemics + insulin, report Z79.84 and Z79.4;
• for insulin and an injectable non-insulin antidiabetic medication, report Z79.4 and Z79.899; and
• don't report Z79.4 or the temporary use of insulin.

Q I've heard there are changes to the reporting of discarded drugs. What are the details?

A CMS is finalizing regulations for the JW modifier used to report discarded amounts of drugs, and the new JZ modifier for attesting that there were no discarded amounts. Providers are required to report the JW modifier beginning January 1, 2023, and to report the JZ modifier no later than July 1, 2023 in all outpatient settings. The Medicare Administrative Contractors have been instructed to deny claims submitted without the appropriate modifier.

TABLE 2. UPDATED MEDICARE AND HOPD-ALLOWED AMOUNTS

CPT	Short Descriptor	ASC 2022	ASC 2023	HOPD 2022	HOPD 2023
66984	CEIOL	$1,063	$1,101	$2,121	$2,159
15823	Blepharoplasty	$887	$899	$1,749	$1,726
66821	YAG capsulotomy	$261	$276	$514	$531
67036	PP Vitrectomy	$1,919	$1,969	$4,000	$3,996

> "For 2023, providers are instructed to continue billing telehealth claims with the place of service you would have billed for an in-person visit and use modifier -95 to identify telehealth service through 2023 or until the end of the year in which the PHE ends."

This will have a great impact on retina practices, as claims for intravitreal medications will require either JW or JZ.

Q What's the status of the COVID-19 Public Health Emergency and how does it impact our practices?

A At this time, the PHE is still in place. CMS implemented the 151-day extension of Medicare telehealth flexibilities, including:
• allowing telehealth services to be provided in any geographic area and in any originating site setting, including the patient's home;
• allowing certain services to be provided via audio-only telehealth; and
• allowing PTs, OTs, speech-language pathologists and audiologists to provide telehealth services.

For 2023 providers are instructed to continue billing telehealth claims with the place of service you would have billed for an in-person visit and use modifier -95 to identify telehealth service through 2023 or until the end of the year in which the PHE ends.

When the PHE ends, flexibility regarding where the patient receives Medicare telehealth services, as well as where the services originate, will revert back to match the restrictions in place prior to the COVID-19 public health emergency. When that occurs, Medicare reimbursement for mental health telehealth services will again require an in-person visit within six months of initial assessment and every 12 months following. Also, Medicare reimbursement for telehealth visits furnished by physical therapists, occupational therapists, speech language pathologists and audiologists will no longer be allowed. Medicare will no longer cover audio-only visits for physical health encounters, and FQHCs and RHCs will no longer be able to be reimbursed as distant site telehealth providers for non-mental health services.

Q Have there been any developments on office-based surgery?

A In recent years, there's been a growing interest in office-based surgery in ophthalmology. Those in favor cite provider convenience, patient experience and contained costs as some of the advantages. On the other hand, opponents have raised concerns regarding such things as sterility, anesthesia provided in an office-based setting, the quality and maintenance of surgical equipment

and the ability to detect and address complications.

To make OBS possible for most providers, the finances need to make sense. For refractive or cosmetic procedures, or care provided to uninsured patients, this model may work. For services billed to Medicare, there is very little the physician may bill. Medicare allows $124 for an IOL but doesn't pay for—or permit providers to bill patients for—a facility fee, surgical supplies, anesthesia by the surgeon or medications that would be eligible for passthrough payment in an ASC. Also, providers may not create an "overhead fee" and bill the patient for it.

In the response comments in the final ASC rule, CMS states: "… we have concerns about these services being furnished in non-facility settings ... CMS will continue to evaluate whether these services are being furnished in non-facility settings and will consider establishing non-facility values for these services at that time."[2]

Q What changes will Medicare beneficiaries have to deal with this year?

A The 2023 Medicare Part A inpatient deductible is $1,600, up from $1,556 in 2022. The 2023 Part B deductible is $226, down from $233 in 2022. For most patients, the monthly Part B premium is $164.90, a decrease from the previous value of $170.10. Remember, since 2007, beneficiary premiums are based on individual or household income. Roughly 7 percent of people with Medicare pay a higher premium based on their income. The increased premiums range from $164.90/month for individuals who earn more than $97,000/year to $560.50/month for individuals with an annual income over $500,000.[5]

Enrollment in Part C Medicare, or Medicare Advantage, continues to increase. In 2022, 28.4 million out of 58.6 million eligible Medicare beneficiaries (48 percent) were enrolled in a Medicare Advantage plan, which is an increase of two percentage points compared to 2021. The Congressional Budget Office estimates that, by 2023, enrollment will rise to about 61 percent of eligible beneficiaries.

In conclusion, each year brings changes to the coding instructions and reimbursement rates that impact all eye-care professionals. Keeping your staff educated on the current codes and instructions is an important aspect of your compliance efforts. ◀

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2. Medicare Program: Hospital outpatient prospective payment and ambulatory surgical center payment systems and quality reporting programs. Federal Register, 11/23/2022.

3. CMS, HOPD 2023 NFRM Addendum P.

4. CMS, Final 2023 ASCQR Measure Set.

5. CMS Fact Sheet. https://www.cms.gov/newsroom/fact-sheets/2023-medicare-parts-b-premiums-and-deductibles-2023-medicare-part-d-income-related-monthly.

ADVERTISER INDEX

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An older woman with severe vision loss presents at Wills Eye Hospital's E.R.

COLLIN J. RICHARDS, MD, AND MARK L. MOSTER, MD
PHILADELPHIA

Presentation

A 74-year-old African-American female presented to the Wills Eye Emergency Room with a five-day history of severe vision loss in the right eye. The patient noted vision loss upon awakening with progressive worsening. The left eye was unaffected. Review of systems was positive for recent-onset shoulder and hip pain, as well as a chronic toothache. She denied jaw pain, scalp tenderness, fevers, chills, weight loss and tinnitus.

Medical History

The patient's past medical history was significant for type 2 diabetes mellitus, hypertension and hyperlipidemia. The patient recalled a questionable history of glaucoma. Her past surgical history included a cholecystectomy. She was currently taking carvedilol, irbesartan, aspirin and metformin. The patient was a non-smoker, denied drug use, and had a family history of type 2 diabetes mellitus and heart disease.

Examination

Upon physical exam, the patient's vital signs were within normal limits. The eye examination revealed a visual acuity of hand motion OD and 20/40 pinhole to 20/25 OS. Pupils were 6 mm bilaterally with a 2+ relative afferent pupillary defect in the right eye. Intraocular pressure was 16 mmHg OD and 20 mmHg OS. By confrontation visual fields, she exhibited globally depressed visual fields in the right eye and full visual fields in the left eye. Her extraocular motility was full bilaterally. Examination with Ishihara color plates revealed 0/8 OD and 8/8 OS.

Anterior slit lamp examination of both eyes was unremarkable with the exception of 2+ nuclear sclerosis bilaterally. On dilated exam, the right optic nerve was found to have prominent disc edema and pallor *(Figure 1)*. The left optic nerve had a cup-to-disc ratio of 0.7 with a healthy appearing rim. The rest of her fundus examination was unremarkable.

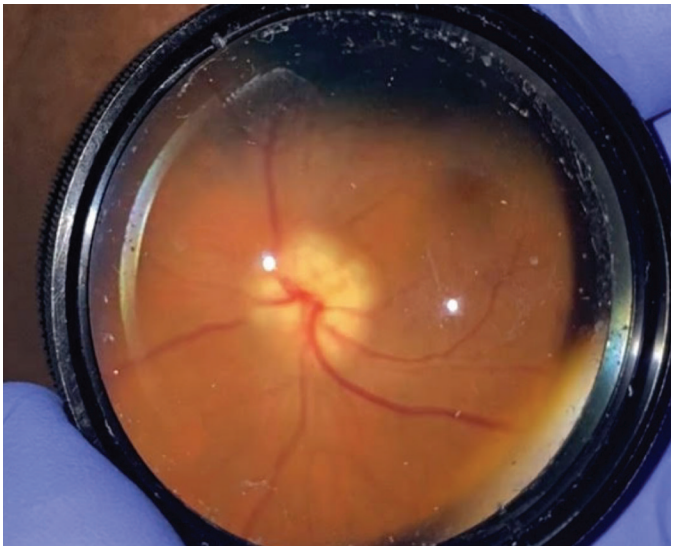

Figure 1. Clinical photograph of the right optic nerve upon presentation showing optic nerve edema.

What's your diagnosis? What further work-up would you pursue? The diagnosis appears on the next page.

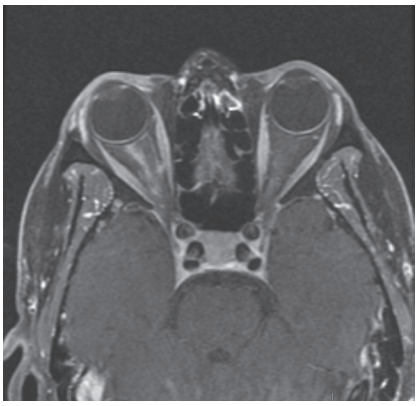

Figure 2. T1-weighted post-contrast MRI showing linear enhancement of the right optic nerve sheath complex.

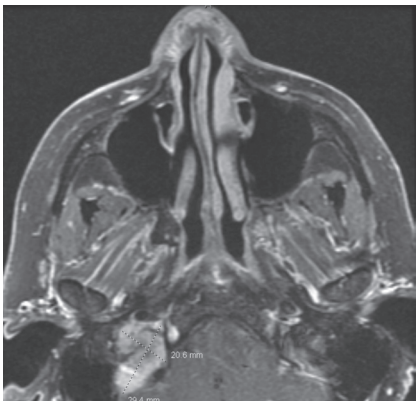

Figure 3. T1-weighted post-contrast MRI showing isointense mass in the right jugular foramen.

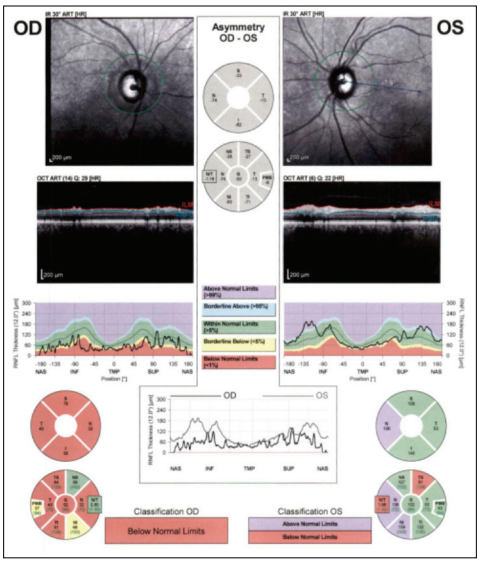

Figure 4. OCT RNFL of both eyes, showing diffuse thinning of the right eye.

Work-up, Diagnosis and Treatment

Based on the findings, a differential diagnosis for severe, unilateral vision loss with associated optic nerve edema was considered. Included in this differential were arteritic anterior ischemic optic neuropathy, non-arteritic ischemic optic neuropathy, meningioma, infiltrative neoplasm, sarcoidosis, Lyme disease, tuberculosis, syphilis and fungal infection. The initial lab work-up included the following: erythrocyte sedimentation rate; C-reactive protein; complete blood count with differential; anti-myelin oligodendrocyte antibody; anti-aquaporin-4 antibody; ACE level; syphilis reverse sequence screening; ANCA antibody panel; ANA panel; IgG4 level; Lyme serologies; and interferon-gamma release assay.

The patient underwent MRI brain and orbits with and without contrast, MRA head without contrast, orbital Doppler ultrasonography and chest X-ray. Her imaging revealed right peripheral optic nerve sheath enhancement *(Figure 2)*. This finding was most compatible with infectious, inflammatory and vasculitic etiologies, although meningioma was also considered as a possibility. Imaging also revealed a right jugular foramen mass, most consistent with glomus jugulare tumor *(Figure 3)*, as well as right corona radiata and internal capsular subacute infarcts. MRA revealed no flow abnormalities and no visualized aneurysms.

Orbital Dopplers revealed an elevated right disc with no vascular flow abnormalities. The ESR was 38, CRP was 0.80, and platelet count was 393, all of which were within the normal range when adjusted for age and gender. The remainder of her laboratory workup detailed above was within normal limits.

This patient's history and examination were most concerning for arteritic anterior ischemic optic neuropathy, though the diagnosis was confounded by the presence of an ipsilateral glomus jugulare lesion and normal inflammatory markers. Otolaryngology was consulted for evaluation of the glomus jugulare lesion, which they assessed to be benign and chronic. The patient was admitted for stroke work-up and started on pulse-dose steroids with 250 mg of methylprednisolone every six hours. A temporal artery biopsy was performed, and the pathology was consistent with a diagnosis of giant cell arteritis. The patient completed five days of pulse-dose steroids and was discharged on 80 mg of oral prednisone.

On follow-up exam four weeks later, there was light perception vision in the right eye and stable vision in the left eye. Funduscopic examination of the right eye revealed a cup-to-disc ratio of 0.99, pallor and a thin rim circumferentially. The remainder of her eye examination was unchanged. Ocular coherence tomography revealed severe thinning of retinal nerve fiber layer and ganglion cell layer in the right eye, with normal thickness of the left eye (*Figures 4 and 5*).

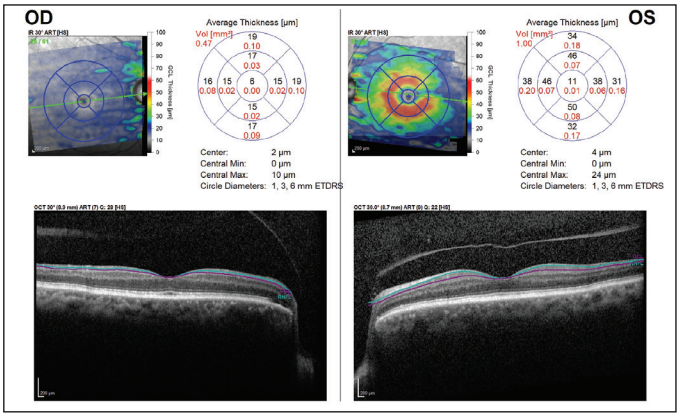

Figure 5. Ganglion cell analysis shows profound GCL loss of the right eye.

Discussion

This case highlights some key GCA take-home points:

• ***Definition and epidemiology.*** Anterior ischemic optic neuropathy is defined as "ischemia to the anterior part of the optic nerve, which is supplied by the posterior ciliary artery circulation."[1] Arteritic anterior ischemic optic neuropathy is defined as a vasculitis predominantly caused by Giant Cell Arteritis.[2] GCA was first described in 1932 and is currently defined as granulomatous arteritis that predominantly affects the aorta and/or its major branches, predominantly the carotid and vertebral arteries, often involving the temporal artery.[3,4] A recent meta-analysis estimates the pooled prevalence of GCA at 51.74 cases per 100,000 and the incidence at 10 cases per 100,000 for patients over 50, with those from Scandinavia disproportionately affected.[5] With an incidence of 4.62 per 100,000 among Africans, our patient's racial demographic group placed her at lower statistical risk for GCA; however, it's imperative to evaluate all patients with signs of GCA, regardless of race.[5,6]

• ***Pathogenesis.*** GCA is a vasculitis that affects medium and large-sized arteries.[2] It's a result of T-cell and macrophage activation, resulting in a granulomatous pan-arteritis with intimal hyperplasia and occlusion of the vascular lumen.[7] The ophthalmic manifestations of GCA are numerous and include AAION, APION, amaurosis fugax, retinal artery occlusion, cotton-wool spots, choroidal ischemia, anterior segment ischemia, extraocular muscle ischemia and motility disorders; ocular ischemic syndrome, and orbital inflammatory syndrome, with AAION being the most common.[8,9]

• ***Diagnosis.*** The 2022 American College of Rheumatology/EULAR classification for GCA requires patients to be older than 50, and includes the following symptoms and diagnostic criteria: morning stiffness in the shoulders and/or neck; sudden visual loss; jaw/tongue claudication; temporal headache; scalp tenderness; elevated ESR; elevated CRP; positive temporal artery biopsy; bilateral axillary involvement; and FDG-PET activity throughout the aorta.[10] The importance of the recommendation for TAB is underscored in this clinical case, as the diagnosis of GCA wouldn't have been definitively made without a positive biopsy based on the ACR criteria.[11]

Ultrasound has been shown to be a useful adjunct in diagnosis, with elevated resistance on color duplex ultrasound of the temporal PCAs having a reported sensitivity of 86 percent and a specificity of 96 percent, with elevated resistance within the nasal PCA performing similarly well.[12] In our case, orbital ultrasound was read as normal, highlighting the importance of maintaining a high clinical suspicion for GCA in cases where the history and clinical examination are concerning. A recent prospective study evaluating the sensitivity of color Doppler ultrasound of the temporal artery places the sensitivity much lower than orbital dopplers, at 5.1 to 30.8 percent.[13]

Reaching the diagnosis of GCA for this patient was complicated by the discovery of an incidental skull-base lesion and the presence of normal inflammatory labs. The sensitivity of a positive TAB for an elevated ESR and CRP is 86.9 and 84.1 percent, respectively. Only 4 percent of patients with normal ESR and CRP had a positive TAB for GCA.[14] Our patient falls into this category, as the team's clinical suspicion for GCA was high and a TAB was pursued despite normal inflammatory labs.

• ***Treatment and clinical course.*** It's currently recommended to immediately treat suspected GCA with high dose glucocorticoids. Among those with acute or intermittent visual loss, it's recommended to initiate pulse-dose, intravenous methylprednisolone.[15] Studies place the risk of relapse during the course of GCA treatment between 40 to 79 percent.[16,17] Continued monitoring of patients with GCA is important, given the risk of relapse and further vascular complications, though the utility and timing of imaging and laboratory markers aren't well-established.[18]

In summary, a 74-year-old woman presented with a clinical picture concerning for GCA given her severe, unilateral vision loss and optic nerve edema with pallor. The treatment team maintained a high clinical suspicion for GCA despite normal inflammatory markers and orbital duplex ultrasonography. MRI of the brain and orbits and a temporal artery biopsy proved useful diagnostic techniques to confirm the diagnosis of GCA. ◀

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Ulcerative keratitis can occur. Patients should be monitored for resolution of epithelial defects.

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These are not all of the side effects of the corneal collagen cross-linking treatment. For more information, go to www.livingwithkeratoconus.com to obtain the FDA-approved product labeling.

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REFERENCE: 1. Photrexa [package insert]. Waltham, MA: Glaukos, Inc; 2016.

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