Wills Eye Resident Series: An older man presents with a vitreous hemorrhage, *p. 94*

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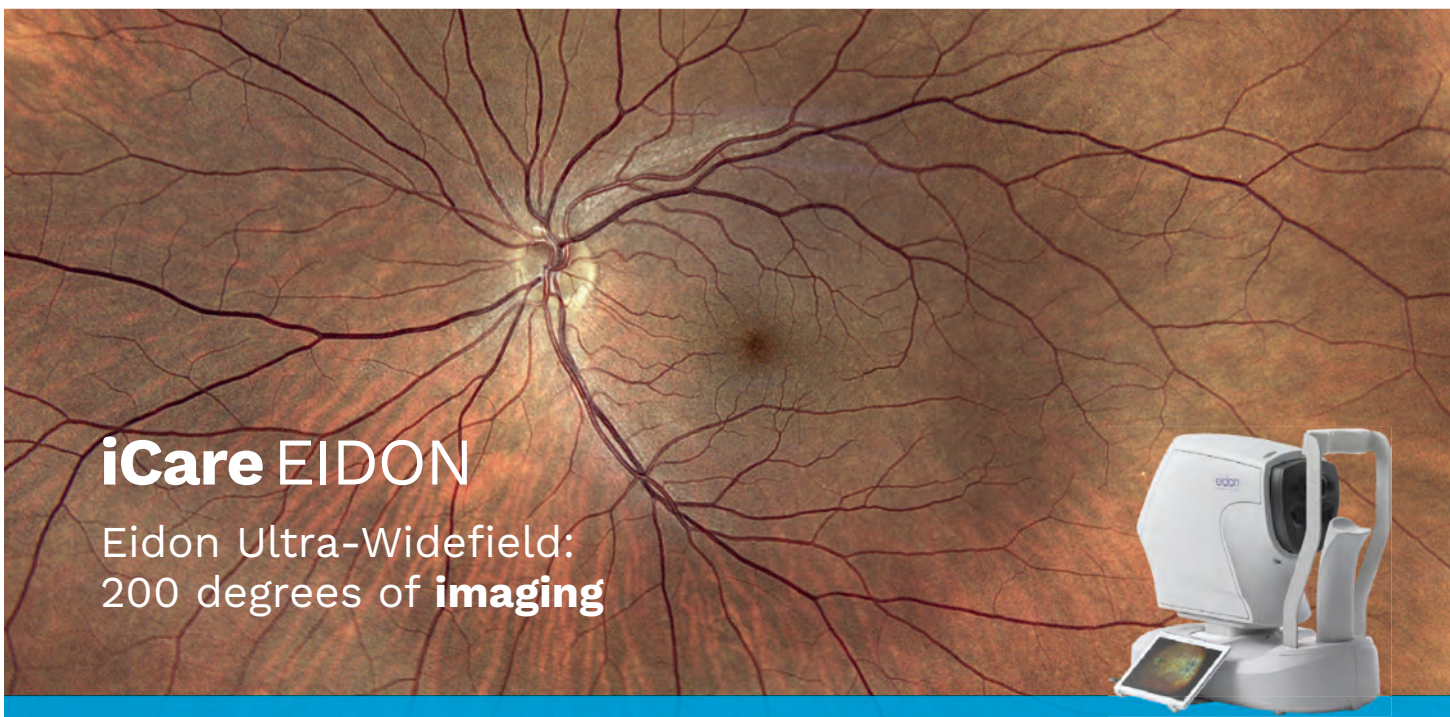

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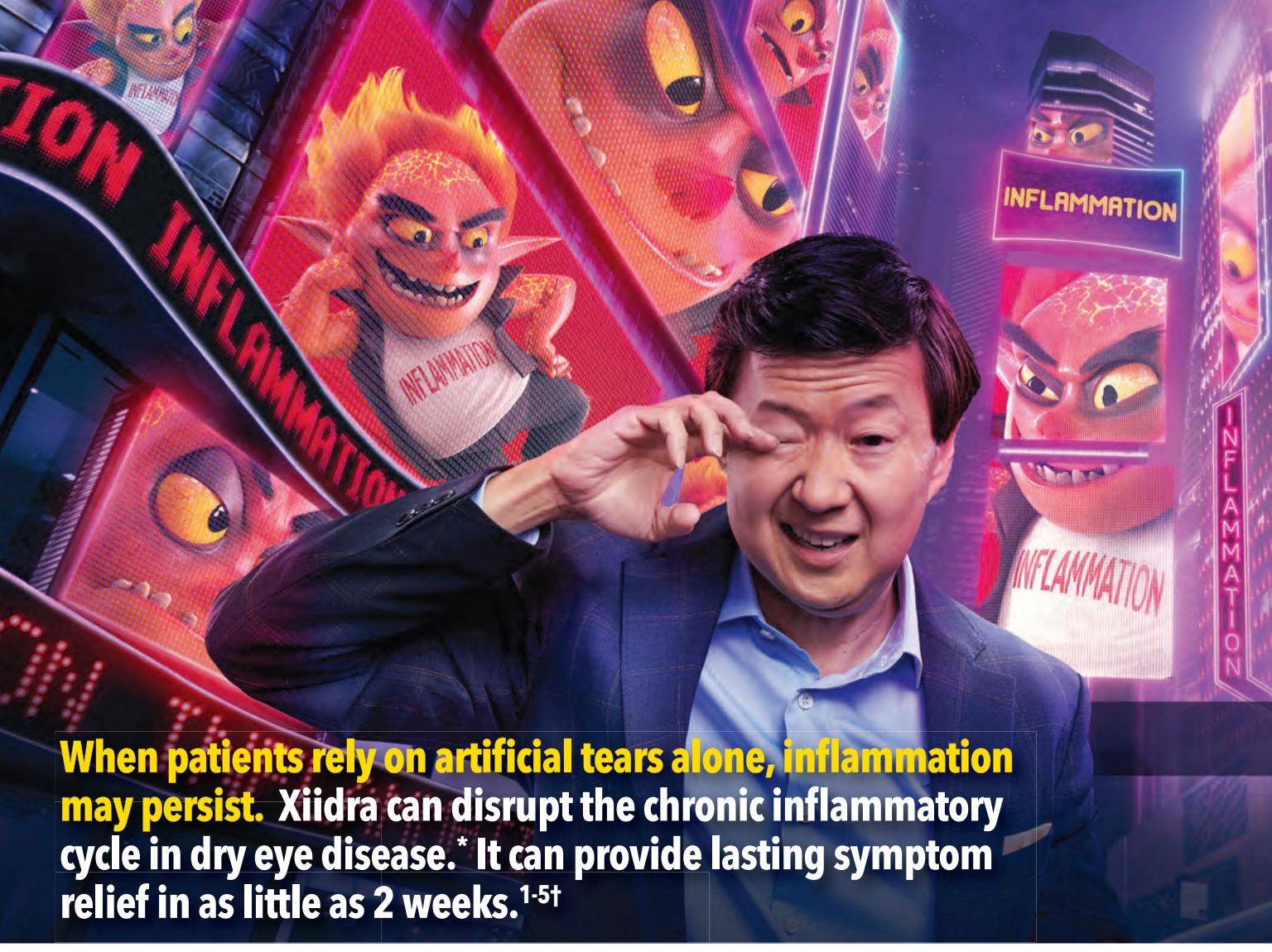

When patients rely on artificial tears alone, inflammation may persist. Xiidra can disrupt the chronic inflammatory cycle in dry eye disease.* It can provide lasting symptom relief in as little as 2 weeks.[1-5†]

*Xiidra blocks LFA-1 on T cells from binding with ICAM-1 that may be overexpressed on the ocular surface in dry eye disease and may prevent formation of an immunologic synapse which, based on in vitro studies, may inhibit T-cell activation, migration of activated T cells to the ocular surface, and reduce cytokine release. The exact mechanism of action of Xiidra in DED is not known.[1,2,5]

† 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. The mean age was 59 years (range, 19-97 years). The majority of patients were female (76%). 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 to 4) and symptoms (based on patient-reported EDS on a visual analogue scale of 0 to 100). 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. Effects on signs of dry eye disease: at day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 out of the 4 studies.[1]

Indication

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

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

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East Hanover, New Jersey 07936-1080

xiidra® (lifitegrast ophthalmic solution) 5%

Dry eyes deserve a change

Important Safety Information (cont)

- 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.
- 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 Full Prescribing Information on adjacent page.

References: 1. Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020. **2.** Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II Pathophysiology Report. *Ocul Surf*. 2017;15(3):438-510. **3.** US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed May 25, 2021. https:/www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **4.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017;15(3):575-628. **5.** Pflugfelder SC, Stern M, Zhang S, Shojaei A. LFA-1/ICAM-1 interaction as a therapeutic target in dry eye disease. *J Ocul Pharmacol Ther*. 2017;33(1):5-12.

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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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SEPTEMBER 2022

New Tech Shows Promise for Evaluating Glaucoma

When cells are stressed by a disease such as glaucoma, their mitochondria produce elevated levels of flavoprotein fluorescence. FPF mapping, a new, non-invasive ocular imaging technology, measures the FPF levels in the eye, providing a way to evaluate the level of metabolic oxidative stress the cells are undergoing. This is showing promise as a way to diagnose glaucoma earlier than previously possible, determine whether a therapy has been effective, distinguish between healthy ocular hypertensives and early glaucoma patients, and objectively measure the damage already present in glaucomatous eyes.

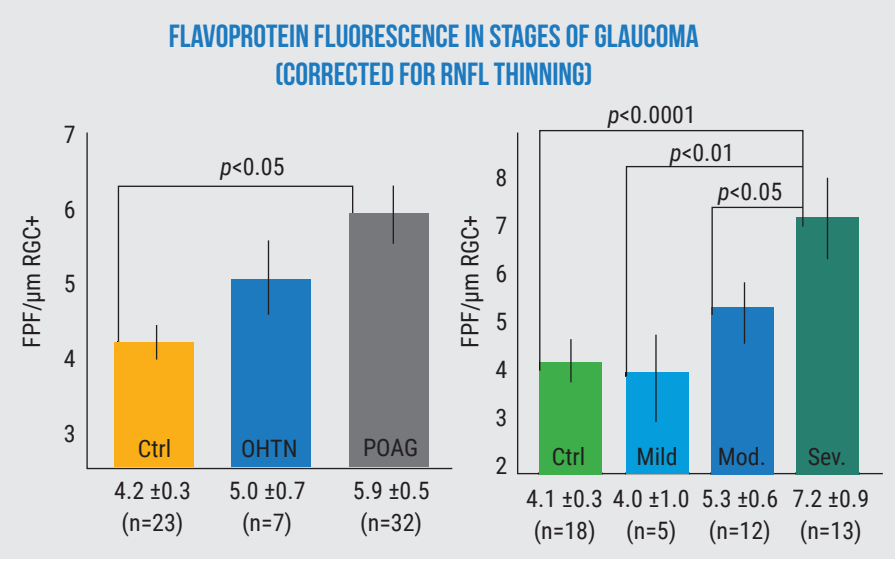
A recently published retrospective, cross-sectional study conducted at the New York Eye and Ear Infirmary of Mount Sinai is the latest to demonstrate the potential utility of this technology.[1] This study measured FPF levels in 86 eyes—50 eyes with POAG and 36 healthy eyes. The data showed that FPF was significantly higher in POAG eyes than in healthy eyes (mean SD: 46.4 ±27.9 versus 28.0 ±11.7, $p<0.001$).

In addition, the researchers noted that in eyes with POAG, the level of FPF correlated with visual field mean deviation ($p<0.001$), visual field pattern standard deviation ($p=0.003$) and cpRNFLT ($p=0.001$). This suggests that FPF mapping might offer a substitute or adjunct to visual field testing. (Visual field testing, which is the current gold standard for measuring visual function, is tedious and unpopular with patients. Its subjective nature contributes to a variety of potential artifacts.)

Richard B. Rosen, MD, vice chair and director of ophthalmology research at the New York Eye and Ear Infirmary and chief of the retina service for the Mount Sinai Health System, was principal investigator for the study. "Levels of flavoprotein fluorescence are measured with a very sensitive detector built into the OcuMet Beacon automated fundus camera," he explains. "This is a commercial device developed by a company called OcuSciences, which is a spinoff from the University of Michigan. The camera has very narrow notch filters, so it detects a very specific wavelength of fluorescence, shorter than the typical lipofuscin autofluoresence most ophthalmologists are familiar with.

"What's interesting is, unlike lipofuscin autofluorescence, which tells us that cells have died because they've stopped fluorescing, the level of FPF changes with the condition of the cells. It increases when the cells are stressed and decreases as they become healthier. The measurement is objective, and studies have indicated that it has good repeatability: Measuring the same

(Continued on p. 8)



Flavoprotein fluorescence increases as glaucoma gets worse and increasingly stresses retinal cells. (All comparisons ANCOVA $p<0.01$.) *Geyman et al, 2018.*[2]

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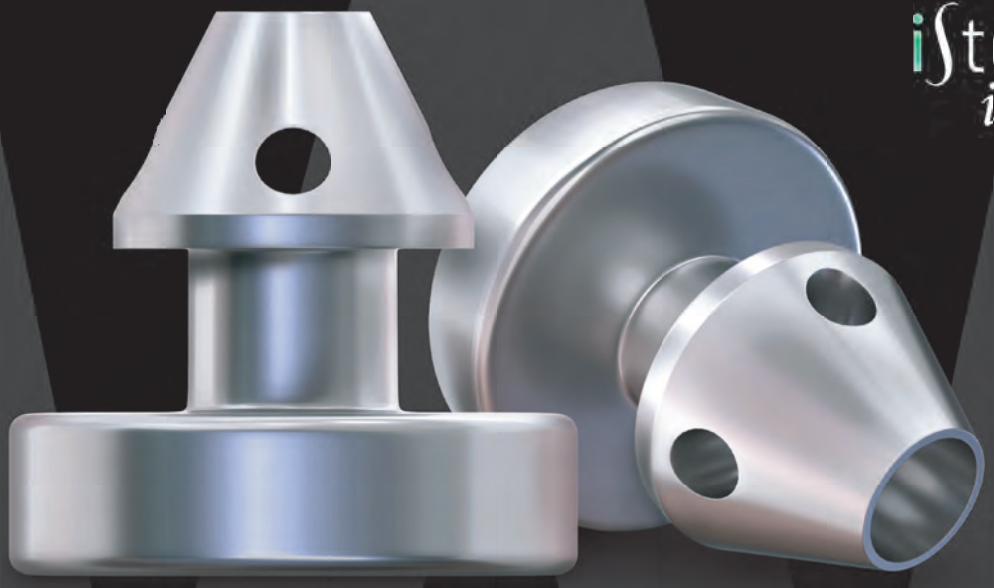

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INDICATION FOR USE. The iStent *inject*® W Trabecular Micro-Bypass System Model G2-W is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma. **CONTRAINDICATIONS.** The iStent *inject* W is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent *inject* W is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent *inject* W have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents. **ADVERSE EVENTS.** Common postoperative adverse events reported in the iStent *inject*® randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent *inject* vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, and adverse events.

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GLAUKOS

(Continued from p. 5)

New Tech for Glaucoma

patient multiple times produces results within a few percentage points each time.

"We've previously published data about a group of diabetic patients receiving anti-VEGF treatment," he continues. "The visual acuity changes in the treated patients correlated with the measured levels of FPF—better than they correlated with the structural changes seen on OCT. Of course, that's always been a problem with OCT: There isn't a great correlation between structural thickness and visual function. That's why the FDA doesn't consider nerve fiber layer thickness to be a good primary endpoint in studies, although it may be used as a surrogate endpoint. In contrast, the FPF measure seems to correlate well with function and functional changes in glaucoma patients. Based on that, it has some promise."

Dr. Rosen says this technology has the potential to be clinically useful in a number of ways. "First, it may help us diagnose glaucoma patients earlier than previously possible," he says. "Frequently, we diagnose glaucoma after damage has occurred. My idea of where this new measure might fit in is if we see early changes suggestive of glaucoma, and the levels of FPF are high, that might make us lean in the direction of making an earlier diagnosis of glaucoma. It's sort of pre-structural-damage metabolic information. This wouldn't be diagnostic by itself, but it could be very useful taken in context.

"Similarly, this technology might allow us to distinguish between ocular hypertensives and early glaucoma patients," he says. "As every ophthalmologist knows, some patients have high pressures but don't really have glaucoma. These ocular hypertensives probably don't need to be treated. A measure that quantifies the metabolic stress that's occurring could make it possible to tell whether or not the high pressure is causing a problem. Studies suggest this technology could provide a means to do that.[2]

> **Another potential use is that this technology might help us determine whether our [glaucoma] therapy was effective. Did the patient respond to our treatment?**
>
> ***— Richard B. Rosen, MD***

"Second, it may help us determine the level of existing damage," he says. "Our latest study looked at a group of glaucoma patients with different levels of the disease and compared their data to normals. It showed that there was good correlation between some recognized standards of visual field changes and FPF levels, making it a potential tool for grading the level of glaucoma.

"Another potential use, as noted earlier, is that this technology might help us determine whether our therapy was effective," he says. "Did the patient respond to our treatment? For example, studies have demonstrated that in a diabetic patient with a high level of FPF, the FPF level goes down after you inject them with anti-VEGF or steroids.[3] In another example, Robert Ritch, MD, did a small study he reported at the annual meeting of the American Glaucoma Society a few years ago, in which he showed that you could decrease the FPF by giving the patient a combination of antioxidant nutraceuticals.

"Finally, this new measure might enable us to tell whether the pressure we've targeted has actually quieted the disease process," he continues. "We know that even if we completely control the pressure, many people will continue to lose vision; this measurement might help us determine how low we need to go. These kinds of uses probably represent the future for this technology."

Dr. Rosen explains that the FPF measure works even in cases of advanced glaucoma, although one confounding factor needs to be taken into account. "In an earlier study[2] we found that the thickness of the nerve fiber layer has an impact on the amount of fluorescence," he explains. "This makes sense physiologically, because if you have less tissue to fluoresce, you'll get less fluorescence. Some of the advanced patients didn't appear to have the higher fluorescence we expected to find until we factored in the thinner nerve fiber layer. When we compensated for that, we found a very good linear correlation between the disease and the FPF level. So it appears that in more advanced patients, we'll need an algorithm that corrects for a thinner nerve fiber layer."

Dr. Rosen says metabolic imaging is an area of great interest right now. "Groups in Iceland and Germany have been championing the idea of measuring metabolic activity with oximetry," he says. "I think measuring metabolic activity will be the future. It will allow us to detect disease without having to wait for a loss of tissue or function. This is the holy grail for retinal imaging.

"At this point, many questions remain to be answered," he admits. "The technology has become much smaller and more affordable since I started working with the prototype 10 years ago, but we still have to maximize the human interface. And we don't know exactly how sensitive the measure is. We've seen patients come in with very high IOPs and high levels of FPF. We bring the IOP to normal and the levels of FPF normalize. But how well does the level of FPF correlate to smaller changes of 3 or 4 mmHg? What's the smallest change in IOP that this

(Continued on p. 40)

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REFERENCES: 1. Ifantides C, Lee J, Rouweyha R, Vital M, Sretavan D. Precision pulse capsulotomy: performance metrics and utility in routine and complex cases. *J Cataract Refract Surg*. 2020 Nov;46(11): 1522-1529. **2.** Thompson V. Streamlined method for anchoring cataract surgery and intraocular lens centration on the patient's visual axis. *J Cataract Refract Surg*. 2018 May;44(5):528-533. **3.** Gundersen K, Potvin R. Clinical results after precision pulse capsulotomy. *Clin Ophthalmol*. 2020 Dec;14:4533-4540.

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PROGRESSION IN GEOGRAPHIC ATROPHY IS RELENTLESS AND IRREVERSIBLE[1-4]

While GA progression may appear to move slowly, it can affect your patients faster than you think[1,4-6]

The consequences of Geographic Atrophy (GA) are too critical to be ignored[7-9]

IN A MEDIAN OF ONLY 2.5 YEARS,
GA lesions encroached on the fovea according to a prospective AREDS study (N=3640)[2]*

2 OUT OF 3 PATIENTS
lost the ability to drive in a median time of <2 years according to a retrospective study (n=523)[10]†

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.

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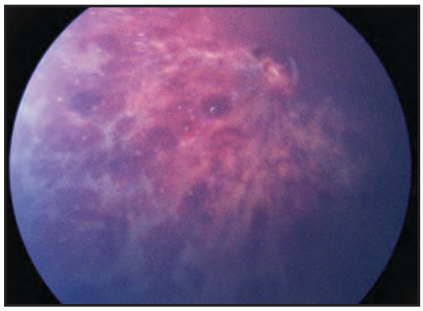

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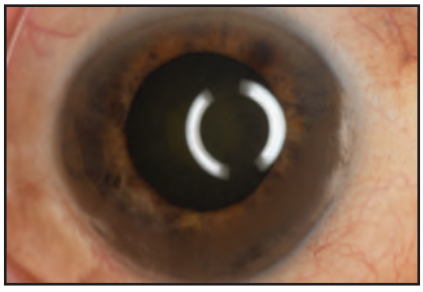

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Photrexa® Viscous (riboflavin 5′-phosphate in 20% dextran ophthalmic solution) and Photrexa® (riboflavin 5′-phosphate ophthalmic solution) are indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia following refractive surgery. Corneal collagen cross-linking should not be performed on pregnant women.

IMPORTANT SAFETY INFORMATION

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

The most common ocular adverse reaction was corneal opacity (haze). Other ocular side effects include punctate keratitis, corneal striae, dry eye, corneal epithelium defect, eye pain, light sensitivity, reduced visual acuity, and blurred vision.

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.

You are encouraged to report all side effects to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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

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REVIEW of OPHTHALMOLOGY

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WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Part-Time Ambivalence

In this month's cover story, physicians and practice management experts share creative ways that ophthalmologists can tackle the growing disparity between the number of patients who need care and the number of physicians available to provide it. They look at it from numerous angles, from the increased use of physician-extenders to ways to expand the number of ophthalmologists. One of the issues they wrestle with is the increase in part-time physicians, and one physician made an interesting assertion: It actually might be unethical for an ophthalmologist to go part time within five years after completing residency without a good reason. The idea is that the country, specifically the taxpayers, funded his or her education with the understanding that the physician would eventually use all this knowledge and skill to serve the community.

This was a striking assertion, and one I'd never thought of—or heard anyone posit—before. Like the servant in the parable who buries the gold his employer gave him rather than use it, multiply it and benefit from it as his fellow servants did with theirs, are part-time physicians wasting their largesse of talent? As with many of life's complex questions, I'm not sure there's an easy answer.

Indeed, the phenomenon of part-time physicians appears to be on the rise. In a 2018 survey, around 10 percent of physicians worked 30 hours or less per week, which was a 16-percent increase from 2012.[1] An older survey of a different group pegged the number of part-time physicians as high as 21 percent.[2]

Cutting back on your availability as a physician definitely makes it tougher to treat the growing number of patients.

However, on the other side of the argument, physician burnout is real: In the 2022 Medscape Physician Burnout and Depression Survey, 47 percent of respondents reported being burned out.[3] A lot of this comes from the increasing amount of time spent away from patient care, grinding through charting and billing, and managing general bureaucratic red tape that saps one's enthusiasm for the work.

The onus on reducing this burnout shouldn't be placed entirely on physicians. CMS and insurers could help ensure more engaged, full-time doctors by easing the endless reimbursement cuts that put financial stress on practices, and by not attempting to enforce onerous dictates such as preauthorization for cataract surgery. Also, as a physician opined in the Medscape survey, health-care organizations can do more to help doctors on the edge. "A call-in counseling service isn't enough," he wrote. "After all, we are the breadwinners for them."

Ophthalmologists are extremely talented people whose patients will need them more than ever in the coming years. Let's hope the organizations that work with them can provide the support they need to answer the call.

— Walter Bethke
Editor in Chief

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- **80% of these patients** remained healed at 1 year (REPARO trial)*[4]

oxervate® (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

* Resolution was evaluated in clinical trials as complete corneal healing, defined as the absence of staining in the lesion area and no persistent staining in the rest of the cornea after 8 weeks of treatment and as <0.5-mm lesion staining at 48-week follow-up.[1-3]

† Key study findings were after 8 weeks of treatment, 6 times daily. REPARO (Study NGF0212): 52 European patients with neurotrophic keratitis (NK) in 1 eye per group; 72% of patients completely healed; vehicle response rate 33.3%. Study NGF0214: 24 US patients with NK in 1 or both eyes per group; 65.2% completely healed; vehicle response rate 16.7%.[2,3]

Important Safety Information

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

In clinical trials, the most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1% to 10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Lactation

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

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in pediatric patients 2 years of age and older is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in children.

INDICATION

OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

To report ADVERSE REACTIONS, contact Dompé U.S. Inc. at 1-833-366-7387 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

References: 1. OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA; Dompé U.S. Inc.; 2019. **2.** Bonini S, et al. *Ophthalmology*. 2018;125:1332-1343. **3.** Pflugfelder SC, et al. *Ophthalmology*. 2020;127:14-26. **4.** Data on File. Clinical Study Report (NGF0212). Dompé U.S. Inc., 2016.

See more clinical data
OXERVATE.com/hcp

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oxervate®
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Brief Summary of full Prescribing Information

Consult the full Prescribing Information for complete product information, available at www.oxervate.com/prescribing-information.

INDICATIONS AND USAGE

OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

General Dosing Information

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

Clinical Studies Experience

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

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Lactation

Risk Summary

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility

Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD).

In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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FDA Approvals Usher in Unique IOL Options

What to know about the new IOLs from AcuFocus and Lenstec, and where they might fit into your practice.

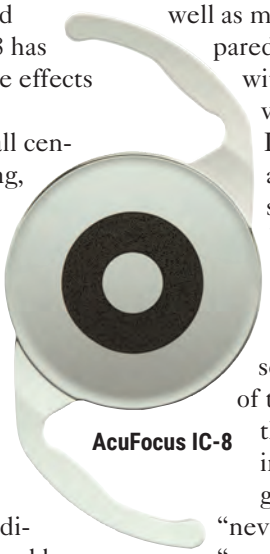
LIZ HUNTER
SENIOR EDITOR

As patients become increasingly particular and demanding about outcomes after cataract surgery, manufacturers have responded with a wealth of IOL options. As each comes through the FDA vetting process and receives approval, surgeons wonder what makes the lens different from the last. The latest to receive their approval are the IC-8 Apthera small-aperture IOL from AcuFocus and the SBL-3 Multifocal IOL from Lenstec, each with its own distinct design and ideal patient population. We spoke with some surgeons who were involved in the FDA study to find out how these lenses perform and what makes them stand out in a competitive marketplace.

AcuFocus IC-8 Apthera Small Aperture IOL

Cataract surgeons will now have a non-toric extended depth of focus IOL for patients with up to 1.5 D of astigmatism at their disposal. The IC-8 Apthera small aperture IOL from AcuFocus was recently FDA approved, and will be available this fall. Intended for implantation in the non-dominant eye, where the fellow eye has already undergone successful monofocal or monofocal toric IOL implantation (targeted for emmetropia),[1] the IC-8 has been shown to mitigate the effects of presbyopia.

The IC-8 features a small central aperture, the FilterRing, to achieve an extended depth of focus. The lens is available in +10 D through +30 D in 0.5-D increments.[1] The refractive target for the IC-8 should be -0.75 D.[1]



AcuFocus IC-8

John Vukich, MD, founder and medical director of Summit Eye Care in Wisconsin, is a medical monitor for AcuFocus and has been involved with developing the prototype for this lens. He says the idea of using a pinhole to collimate light to extend depth of focus and eliminate blur is something all ophthalmologists learn as residents.

"This concept doesn't require a great deal of explanation or leap of faith to understand why it works," Dr. Vukich says. "As a practical matter, it's an idea that's been around forever."

He says this technology gives surgeons a chance to meet the high expectations of cataract patients. "Cataract surgery is not just about removing a cloudy lens. There's an expectation attached to it of having a predictable refractive outcome. Astigmatic correction still requires a toric lens, but now we have an option with a pinhole that will get up to 1.5 D or 1.75 D of correction of astigmatism," says Dr. Vukich. "This has a large landing zone for emmetropia, and doesn't have rotational or alignment issues."

The FDA study revealed the IC-8 group was "statistically superior" in binocular UCIVA and UCNVA, as well as monocular DCIVA, compared to the group implanted with the control IOL.[1] The visual performance of the IC-8 was demonstrated in a study of 105 patients that showed patients achieving UDVA of 20/23, UIVA of 20/24, and UNVA of 20/30 at six months.[2]

Visual symptoms were severe in a low percentage of test subjects, with more than 80 percent of subjects in both the IC-8 and control groups reporting they "never experienced symptoms," "experienced symptoms but not bothered at all," or were "a little bothered" by visual symptoms at 12 months postop.[1]

Dr. Vukich says patient satisfaction is high with this lens. "What you don't get with the IC-8 are glare, ring halos, spider web halos, and all of the things that happen with the other multifocals and other methods of providing depth of focus," he says. "Those lenses all have some optical aberrations that patients can notice. Many patients can disregard or ignore them, but there are certain patients who are never able to accept or adapt to the glare or halos with multifocality. So, if you can get rid of the aberrations that make patients unhappy or con-

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.

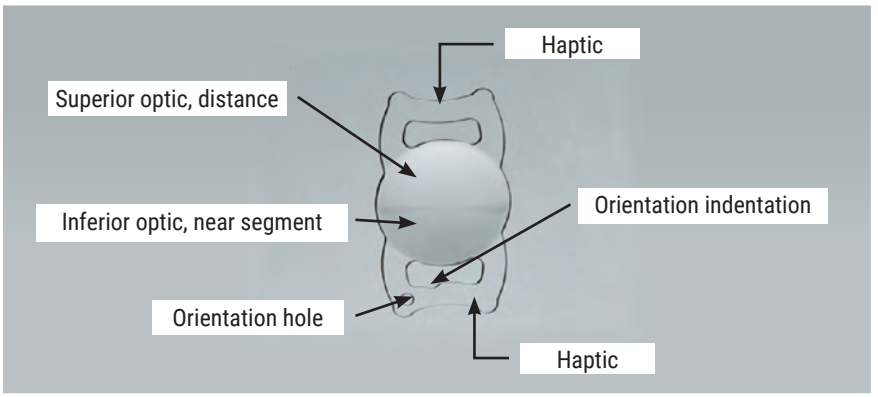
cerned, and with a lens that neutralizes up to 1.75 D of astigmatism, that's a real win."

Dr. Vukich believes this lens is a good option for any patient, and adds there is good evidence from international use that this lens works well for patients who have atypical corneas, corneal scars or are post-LASIK/post-PRK. "It's not as easy to get a predictable outcome on those individuals, so I think this lens will provide a level of comfort with its big range. Even if we can get close postoperatively, the patient will still have good vision," he says.

Adding to the IC-8's strengths is its lack of learning curve, Dr. Vukich says. "Any surgeon who's comfortable placing a one-piece acrylic lens in the capsular bag—and that should really be any cataract surgeon—will have no barrier to entry in terms of learning how to use this lens," he opines.

The IC-8 is contraindicated for patients with a dilated pupil size less than 7 mm, in order to mitigate risks of secondary surgical interventions and IOL damage due to difficulty performing YAG laser treatments.[1] Subjects with a history of retinal disease, high myopia, diabetes, macular disease, sickle cell disease, retinal tear and detachment, uveitis or retinal vein occlusion, or who are predisposed to retinal disease are not recommended for this lens.[1]

Although there's been no shortage of IOLs coming to market, Dr. Vukich says it's OK to have more than "one club in your bag," so to speak. "There will be slight preferences that will tip the scale one way or the other, but having choice is better than not having choice," he says. "We're trying to get as close as we can to the natural function of a young human lens. We're not there yet, but we're getting closer, and this is a step in the right direction."



The Lenstec SBL-3 has a segmented optic with two power zones: The top is powered for distance and the bottom for near, much like bifocal glasses.

Lenstec SBL-3 Multifocal IOL

Another newcomer to the IOL playing field is the SBL-3 (segmented bifocal lens) from Lenstec, whose segmented optic design will be the only one of its kind in the United States, according to the company.[3] Its stated indications for use include improvement of near vision, while maintaining comparable distance and intermediate visual acuity, resulting in less reliance on spectacles.[4]

Unlike other multifocal IOLs, the SBL-3 has a segmented optic with two power zones: The top is powered for distance, the bottom for near, much like bifocal glasses. There's also a half-power ring around the near portion of the optic. The SBL-3 is available in 0.25-D increments with a power range of +15 to +25 D, and 0.50-D increments for +25 to +30 D.[4]

This lens has been available elsewhere, including the United Kingdom, Canada, South America and Germany. Many surgeons in the United States have been hearing from international colleagues about the SBL-3's reported reduction of dysphotopsias, as well as how quickly patients adapt.

T. Hunter Newsom, MD, founder of Newsom Eye & Laser Center in Tampa, got his chance to work with the IOL as a part of the FDA study.

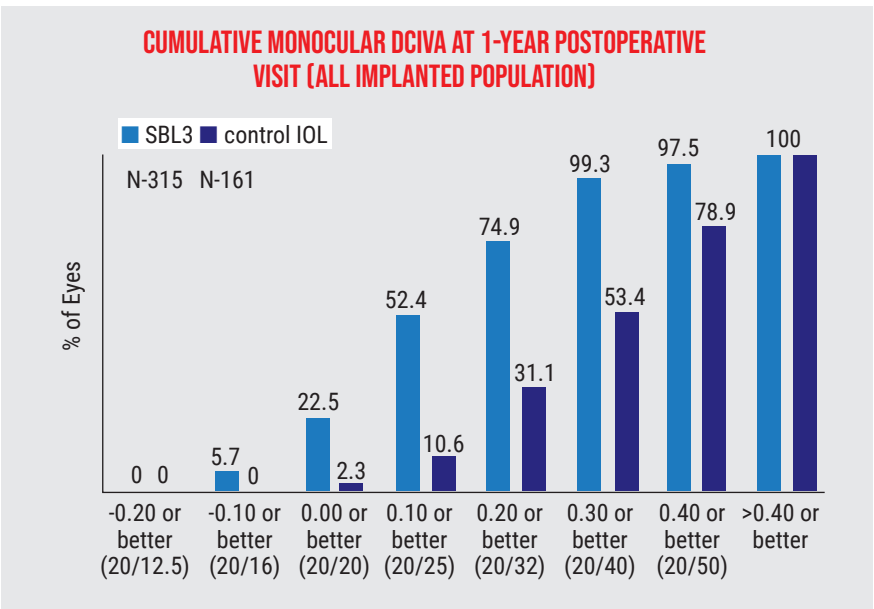


Figure 1. In the FDA study, the SBL-3 group showed an improvement in intermediate vision (93.9 percent) over the control (45.3 percent).[4]

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†VISCOAT® showed significantly lower superior corneal endothelial cell loss at 16 weeks post-op compared to HEALON*; n=59, P<0.01.
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"We'd been hearing that patients were getting really good near and distance vision, and that the ability to see up close could occur very quickly, whereas with other multifocal technologies there is always that neuro-adaptation adjustment time," Dr. Newsom says.

As part of the FDA study, some patients were implanted with a monofocal control IOL, but according to Dr. Newsom, patients could tell almost immediately which lens they'd received. "We'd do the surgery and practically 30 minutes postop patients would say, 'I know I got the bifocal lens because I can read my watch right now,'" he recounts. "It wasn't like I had to explain that they would adjust to the vision over the course of three months; it was more like putting on a pair of progressive glasses and very quickly starting to function very well."

The FDA study revealed a "clinically meaningful difference" in the vision outcomes of the two lenses, with the SBL-3 representing a 20/25 mean visual acuity, versus 20/80 in the control group.[4] When asked about using vision correction options (spectacles, contact lenses, increased font size on electronic devices, etc.), 93.3 percent of the SBL-3 group reported a reduced use, versus 25.5 percent in the control group. The SBL-3 group also had a much greater improvement in intermediate vision (93.9 percent) than the control group (45.3 percent).

Dr. Newsom says the SBL-3 aims to improve on some of the negative aspects of multifocal IOLs in general. "The problem with current multifocal technology is that you trade distance vision to gain at the near end, and you have a loss of nighttime quality vision," he says. "The Vivity IOL, uses a novel approach that stretches the light, but it doesn't give you as much near vision," he says. "The SBL-3 uses the same technology as progressive spectacles. It's not really special when you think about it that way, but it is special because you have to appreciate the engineering that went into creating a lens that's one shape on top and another shape on the bottom, put together. All the other lenses use rings to make distance and near happen, and they have to do it circumferentially."

Patients who are already wearing progressives would be natural fits for this lens, he continues, and he's even willing to use the SBL-3 on patients who need good night-driving vision. "We put someone in the study who's a professional long-haul truck driver and they're still doing well at near and distance with no glasses," he says. "I don't think I would've ever put previous multifocal technology into someone like that," Dr. Newsom says. "I think this lens is going to be more forgiving than our current multifocal technology and extend the patient-selection criteria."

Dr. Newsom notes that there are pros and cons with the lens, as with anything else. "The lens doesn't come in a toric, so if a patient has a large amount of astigmatism, you might have to dust off your LRI skills, which we've all done for years, but you need to be able to control the astigmatism with it," he says. "And you may need to do adjustments or rotations to fine tune the refraction or results, just like we do with the current multifocal IOLs. You have to learn how this fits into your practice."

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DISCLOSURES

Dr. Vukich is a consultant and medical monitor for AcuFocus. **Dr. Newsom** is a consultant for Lenstec.

Important Product Information for DUOVISC® OVD

Description: DuoVisc® Viscoelastic System is designed to provide two Viscoelastic materials with different physico-chemical properties that can be used differently and/or sequentially to perform specific tasks during a cataract procedure. DuoVisc® Viscoelastic System consists of VISCOAT® Ophthalmic Viscosurgical Device and ProVisc® Ophthalmic Viscosurgical Device. **Caution:** Federal (USA) law restricts this device to sale by, or on the order of, a physician.

Description: VISCOAT® (Sodium Chondroitin Sulfate – Sodium Hyaluronate) Ophthalmic Viscosurgical Device. **Indications:** VISCOAT® OVD is indicated for use as an ophthalmic surgical aid in anterior segment procedures including cataract extraction and intraocular lens (IOL) implantation. VISCOAT® OVD maintains a deep anterior chamber during anterior segment surgeries, enhances visualization during the surgical procedure, and protects the corneal endothelium and other ocular tissues. The viscoelasticity of the solution maintains the normal position of the vitreous face and prevents formation of a flat chamber during surgery. **Warnings/Precautions:** Failure to follow assembly instructions or use of an alternate cannula may result in cannula detachment and potential patient injury. Precautions are limited to those normally associated with the surgical procedure being performed. Although sodium hyaluronate and sodium chondroitin sulfate are highly purified biological polymers, the physician should be aware of the potential allergic risks inherent in the use of any biological material. **Adverse Reactions:** VISCOAT® OVD has been extremely well tolerated in human and animal studies. A transient rise in intraocular pressure in the early postoperative period may be expected due to the presence of sodium hyaluronate, which has been shown to affect such a rise. It is therefore recommended that VISCOAT® OVD be removed from the anterior chamber by thorough irrigation and/or aspiration at the end of surgery to minimize postoperative IOP increases. Do not overfill anterior chamber. **ATTENTION:** Please refer to the Directions for Use for a complete listing of indications, warnings and precautions.

Description: ProVisc® (Sodium Hyaluronate) Ophthalmic Viscosurgical Device. **Indications:** ProVisc® OVD is indicated for use as an ophthalmic surgical aid in the anterior segment during cataract extraction and intraocular lens (IOL) implantation. Ophthalmic viscoelastics serve to maintain a deep anterior chamber during anterior segment surgery allowing reduced trauma to the corneal endothelium and surrounding ocular tissues. They help push back the vitreous face and prevent formation of a flat chamber during surgery. **Warnings/Precautions:** Postoperative increases in intraocular pressure have been reported with sodium hyaluronate products. The IOP should be carefully monitored and appropriate therapy instituted if significant increases should occur. It is recommended that ProVisc® OVD be removed by irrigation and/or aspiration at the close of surgery. Do not overfill anterior chamber. Although sodium hyaluronate is a highly purified biological polymer, the physician should be aware of the potential allergic risks inherent in the use of any biological material; care should be used in patients with hypersensitivity to any components in this material. Cannula assembly instructions should be followed to prevent patient injury. **Adverse Reactions:** Postoperative inflammatory reactions such as hypopyon and iritis have been reported with the use of ophthalmic viscoelastics, as well as incidents of corneal edema, corneal decompensation, and a transient rise in intraocular pressure. **ATTENTION:** Please refer to the directions for use for a complete listing of indications, warnings and precautions.

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A Not-So-Slow Simmer

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

Hot enough for you? It is for many people around the world. 2022 is on track to again set new records, as have most of the past 10 years. And it's getting worse. As I write this, more than half of the United States is in severe drought, and most of the country is having yet another heatwave, with new high temperatures recorded across the country. Europe has been baking all summer, and in India and the Arabian Peninsula they're seeing temperatures they have never felt before: over 120 F. These temperature peaks are above that which humans can survive outdoors. And while air conditioning works, it's not universally available, uses huge amounts of energy, heats the air around it and doesn't help if you have to work outdoors.

The implications of further warming are scary. The melting of the glaciers is dumping huge amounts of water into the ocean, and vast areas of the planet are becoming uninhabitable, resulting in mass migrations of people and a disruption of the world economy. Fluctuating weather patterns produce more intense storms as the oceans warm and, conversely, fertile areas turning into deserts is a new reality. We're seeing this writ large around the world with 100-year storms occurring almost every year. Humans can adapt, but at what cost? I read an interesting piece a year ago about how humans are built to tolerate cold much better than heat. Our physiology can withstand colder temps, and we can modify our protective clothing and still function normally. In heat there isn't much to do but take off clothes or go inside. And the danger in going from 90 to 100 degrees Fahrenheit is exponential.

While it's clear the planet is going through a warming cycle, what isn't universally agreed upon is the cause. Most scientists are certain it's from human activity. But in our current times, science isn't the lodestone it used to be. People who have no education in these matters quickly shift from being armchair virologists to armchair climate scientists. But I'll posit that it doesn't matter whether you believe human activity is the cause of climate change. I think everyone can agree that increasing atmospheric levels of carbon dioxide and methane aren't good. So even if they're not the sole or major cause of warming, controlling them is something we can do to try to help mitigate the change. What we need to do, for a host of reasons, is move away from burning hydrocarbons. I'm old enough to remember what the air looked like before we started controlling pollution. We can all appreciate clean air, and the cleaner the better. We can also appreciate that extracting coal, oil and gas is a messy process. Oil spills devastate beaches and other habitats, fracking uses massive amounts of precious fresh water and results in huge ponds of toxic waste. And don't forget that hydrocarbons have other unique uses in manufacturing, and it would be nice to leave some for future generations instead of burning it all. A good start has been made in switching to other energy sources, but it's neither enough, nor perfect. We must push harder. Yes, there is a cost to doing this, but there is also a huge cost to doing nothing.

You may be wondering why I'm writing about this. None of this is new, and it's been covered extensively by writers far better than I. No, I don't think I'm going to change any minds or sell any Teslas. But in the grand scheme of what keeps me up at night and gives me this sense of foreboding, the future habitability of the planet ranks right up there. As has been said before, there is no Planet B. Though escaping to Mars appeals to the sci-fi loving side of me, it's not really an answer to the problem. We can do better. We have to. ◀

This article has no commercial sponsorship.

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

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MEDICARE Q&A

2023 ICD-10 and New Drug Codes

An update on the new diagnosis codes for ophthalmology as well as codes for new therapeutic options.

Q Are there any new codes recently released that I should know about? If so, when do we use them?

A We have the new ICD-10 codes and a couple of new HCPCS "J" codes. The J codes must be used immediately for Medicare; most other payers will follow suit. ICD-10 codes for 2023 were recently released by the Centers for Medicare & Medicaid Services. As always, they are for use each year, starting in October. That means you must begin using any new diagnosis codes or relevant coding guidance in October 2022—don't wait until January of 2023 to start.

Q What eye drugs are affected by the new codes?

A CMS recently announced the expiration of two temporary C codes for a couple of relatively new drugs and their replacement with permanent J codes. In the first quarter "HCPCS Coding Cycle" announcement by CMS, they considered code applications and then issued new codes if the action was approved. For eye care, the codes affect Susvimo (Genentech) and Xipere (Bausch + Lomb)—and the new codes must be used as of July 1, 2022 for Part B Medicare. It's likely that other payers will follow suit and demand the new codes, too—but some may lag a month or two, so you should check.

Q What are the codes affected for Susvimo?

A CMS noted the following Final Decision for the permanent J code Susvimo:

1) Establish new HCPCS Level II code J2779, "Injection, ranibizumab, via intravitreal implant (Susvimo), 0.1 mg" Effective: 7/1/2022

2) Discontinue existing HCPCS Level II code C9093, "Injection, ranibizumab, via intravitreal implant (susvimo), 0.1 mg" Effective: 6/30/2022

Q How do I bill for Susvimo? Is it different in the office than in a facility?

A Beginning July 1, 2022, billing will be as follows for Susvimo:

The recommended dose from the FDA package insert is 2 mg (0.2 ml of 100 mg/ml). That applies to both the expired C9093 code and the new J2779 code HCPCS code since each is written as "per 0.1 mg." Importantly, you can be paid for the entire vial of this single-use vial (even for the wasted portion), but you'll need two lines on the claim for the drug to accomplish that. You can't put Susvimo on a single line with 100 units; that's counter to already established CMS instructions when there's billable wastage. Bill the administered dose as a line on the claim with 20 units and use a separate line for the unused (wasted) drug, which will show as a second line with JW modifier and 80 units.

No matter the location, the surgeon's op note for the Susvimo injection needs to show the administered and wasted doses separately. It also must show the lot number and expiration date for the vial used. The NDC # (10-digit 50242-078-12) for SUSVIMO goes in box 19 of the CMS-1500 form.

If this is done at a facility, the facility bills for the drug (not the surgeon). Both the facility and the surgeon get to bill for the injection piece.

Q What codes are used for Xipere?

A For Xipere, the Final Decision and codes are as follows:

1) Establish new HCPCS Level II code J3299, "Injection, triamcinolone acetonide (Xipere), 1 mg" Effective: 7/1/2022

2) Discontinue existing HCPCS Level II code C9092, "Injection, triamcinolone acetonide, suprachoroidal (Xipere), 1 mg" Effective: 6/30/2022

Q How do I bill for Xipere? Is it different in the office than in a facility?

A Since the recommended dose in the FDA approval for Xipere is 4 mg (0.1 ml of the 40 mg/ml single use vial), billing will be as follows:

One line with the administered dose with four units, and a second line with the wasted drug with JW modifier and 36 units. As above, you can't put all 40 units of the drug on a single line. Since you're paid for an entire vial, the op notes should reflect the doses given and wasted as well as the lot number and expiration dates. The NDC for Xipere (10 digit 71565-040-25) goes in box 19. As with Susvimo above, if this is done at a facility, the

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Mr. Larson is a senior consultant at the Corcoran Consulting Group and is based in Tucson, Arizona. He can be reached at plarson@corcoranccg.com.

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†Out of 124 patients from the clinical study, 122 responded that they would have LASIK again.

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For Important Product Information about Contoura® Vision, please refer to the adjacent page.

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CONTOURA® VISION

WAVELIGHT® EXCIMER LASER SYSTEMS IMPORTANT PRODUCT INFORMATION

This information pertains to all WaveLight® Excimer Laser Systems, including the WaveLight® ALLEGRETTO WAVE®, the ALLEGRETTO WAVE® Eye-Q and the WaveLight® EX500. **Caution**: Federal (U.S.) law restricts the WaveLight® Excimer Laser Systems to sale by or on the order of a physician. Only practitioners who are experienced in the medical mangement and surgical treatment of the cornea, who have been trained in laser refractive surgery (including laser calibration and operation) should use a WaveLight® Excimer Laser System. **Indications**: FDA has approved the WaveLight® Excimer Laser systems for use in laser-assisted in situ keratomileusis (LASIK) treatments for: the reduction or elimination of myopia of up to - 12.00 D and up to 6.00 D of astigmatism at the spectacle plane; the reduction or elimination of hyperopia up to + 6.00 D with and without astigmatic refractive errors up to 5.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of + 6.00 D; the reduction or elimination of naturally occurring mixed astigmatism of up to 6.00 D at the spectacle plane; and the wavefront-guided reduction or elimination of myopia of up to -7.00 D and up to 3.00 D of astigmatism at the spectacle plane. In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of up to -9.00 D of myopia, or for the reduction or elimination of myopia with astigmatism, with up to -8.00 D of myopia and up to 3.00 D of astigmatism. The WaveLight® Excimer Laser Systems are only indicated for use in patients who are 18 years of age or older (21 years of age or older for mixed astigmatism) with documentation of a stable manifest refraction defined as ≤ 0.50 D of preoperative spherical equivalent shift over one year prior to surgery, exclusive of changes due to unmasking latent hyperopia. **Contraindications**: The WaveLight® Excimer Laser Systems are contraindicated for use with patients who: are pregnant or nursing; have a diagnosed collagen vascular, autoimmune or immunodeficiency disease; have been diagnosed keratoconus or if there are any clinical pictures suggestive of keratoconus; are taking isotretinoin (Accutane*) and/or amiodarone hydrochloride (Cordarone*); have severe dry eye; have corneas too thin for LASIK; have recurrent corneal erosion; have advanced glaucoma; or have uncontrolled diabetes. **Warnings**: The WaveLight® Excimer Laser Systems are not recommended for use with patients who have: systemic diseases likely to affect wound healing, such as connective tissue disease, insulin dependent diabetes, severe atopic disease or an immunocompromised status; a history of Herpes simplex or Herpes zoster keratitis; significant dry eye that is unresponsive to treatment; severe allergies; a history of glaucoma; an unreliable preoperative wavefront examination that precludes wavefront-guided treatment; or a poor quality preoperative topography map that precludes topography-guided LASIK treatment. The wavefront-guided LASIK procedure requires accurate and reliable data from the wavefront examination. Every step of every wavefront measurement that may be used as the basis for a wavefront-guided LASIK procedure must be validated by the user. Inaccurate or unreliable data from the wavefront examination will lead to an inaccurate treatment. Topography-guided LASIK requires preoperative topography maps of sufficient quality to use for planning a topography-guided LASIK treatment. Poor quality topography maps may affect the accuracy of the topography-guided LASIK treatment and may result in poor vision after topography-guided LASIK. **Precautions**: The safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for patients with: progressive myopia, hyperopia, astigmatism and/or mixed astigmatism, ocular disease, previous corneal or intraocular surgery, or trauma in the ablation zone; corneal abnormalities including, but not limited to, scars, irregular astigmatism and corneal warpage; residual corneal thickness after ablation of less than 250 microns due to the increased risk for corneal ectasia; pupil size below 7.0 mm after mydriatics where applied for wavefront-guided ablation planning; history of glaucoma or ocular hypertension of > 23 mmHg; taking the medications sumatriptan succinate (Imitrex*); corneal, lens and/or vitreous opacities including, but not limited to cataract; iris problems including , but not limited to, coloboma and previous iris surgery compromising proper eye tracking; or taking medications likely to affect wound healing including (but not limited to) antimetabolites. In addition, safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for: treatments with an optical zone < 6.0 mm or > 6.5 mm in diameter, or an ablation zone > 9.0 mm in diameter; or wavefront-guided treatment targets different from emmetropia (plano) in which the wavefront calculated defocus (spherical term) has been adjusted; In the WaveLight® Excimer Laser System clinical studies, there were few subjects with cylinder amounts > 4 D and ≤ 6 D. Not all complications, adverse events, and levels of effectiveness may have been determined for this population. Pupil sizes should be evaluated under mesopic illumination conditions. Effects of treatment on vision under poor illumination cannot be predicted prior to surgery. **Adverse Events and Complications** Myopia: In the myopia clinical study, 0.2% (2/876) of the eyes had a lost, misplaced, or misaligned flap reported at the 1 month examination. The following complications were reported 6 months after LASIK: 0.9% (7/818) had ghosting or double images in the operative eye; 0.1% (1/818) of the eyes had a corneal epithelial defect. Hyperopia: In the hyperopia clinical study, 0.4% (1/276) of the eyes had a retinal detachment or retinal vascular accident reported at the 3 month examination. The following complications were reported 6 months after LASIK: 0.8% (2/262) of the eyes had a corneal epithelial defect and 0.8% (2/262) had any epithelium in the interface. Mixed Astigmatism: In the mixed astigmatism clinical study, two adverse events were reported. The first event involved a patient who postoperatively was subject to blunt trauma to the treatment eye 6 days after surgery. The patient was found to have an intact globe with no rupture, inflammation or any dislodgement of the flap. UCVA was decreased due to this event. The second event involved the treatment of an incorrect axis of astigmatism. The axis was treated at 60 degrees instead of 160 degrees. The following complications were reported 6 months after LASIK: 1.8% (2/111) of the eyes had ghosting or double images in the operative eye. Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). No adverse events occurred during the postoperative period of the wavefront-guided LASIK procedures. In the Control Cohort, one subject undergoing traditional LASIK had the axis of astigmatism programmed as 115 degrees instead of the actual 155 degree axis. This led to cylinder in the left eye. The following complications were reported 6 months after wavefront-guided LASIK in the Study Cohort: 1.2% (2/166) of the eyes had a corneal epithelial defect; 1.2% (2/166) had foreign body sensation; and 0.6% (1/166) had pain. No complications were reported in the Control Cohort. Topography-Guided Myopia: There were six adverse events reported in the topography-guided myopia study. Four of the eyes experienced transient or temporary decreases in vision prior to the final 12 month follow-up visit, all of which were resolved by the final follow-up visit. One subject suffered from decreased vision in the treated eye, following blunt force trauma 4 days after surgery. One subject experienced retinal detachment, which was concluded to be unrelated to the surgical procedure. **Clinical Data** Myopia: The myopia clinical study included 901 eyes treated, of which 813 of 866 eligible eyes were followed for 12 months. Accountability at 3 months was 93.8%, at 6 months was 91.9%, and at 12 months was 93.9%. Of the 782 eyes that were eligible for the uncorrected visual acuity (UCVA) analysis of effectiveness at the 6-month stability time point, 98.3% were corrected to 20/40 or better, and 87.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: visual fluctuations (28.6% vs. 12.8% at baseline). Long term risks of LASIK for myopia with and without astigmatism have not been studied beyond 12 months. Hyperopia: The hyperopia clinical study included 290 eyes treated, of which 100 of 290 eligible eyes were followed for 12 months. Accountability at 3 months was 95.2%, at 6 months was 93.9%, and at 12 months was 69.9%. Of the 212 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 95.3% were corrected to 20/40 or better, and 69.4% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "much worse" at 6 months post-treatment: halos (6.4%); visual fluctuations (6.1%); light sensitivity (4.9%); night driving glare (4.2%); and glare from bright lights (3.0%). Long term risks of LASIK for hyperopia with and without astigmatism have not been studied beyond 12 months. Mixed Astigmatism: The mixed astigmatism clinical study included 162 eyes treated, of which 111 were eligible to be followed for 6 months. Accountability at 1 month was 99.4%, at 3 months was 96.0%, and at 6 months was 100.0%. Of the 142 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 97.3% achieved acuity of 20/40 or better, and 69.4% achieved acuity of 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: sensitivity to light (52.9% vs. 43.3% at baseline); visual fluctuations (43.0% vs. 32.1% at baseline); and halos (42.3% vs. 37.0% at baseline). Long term risks of LASIK for mixed astigmatism have not been studied beyond 6 months. Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). 166 of the Study Cohort and 166 of the Control Cohort were eligible to be followed at 6 months. In the Study Cohort, accountability at 1 month was 96.8%, at 3 months was 96.8%, and at 6 months was 93.3%. In the Control Cohort, accountability at 1 month was 94.6%, at 3 months was 94.6%, and at 6 months was 92.2%. Of the 166 eyes in the Study Cohort that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 93.4% were corrected to 20/20 or better. Of the 166 eyes in the Control Cohort eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 92.8% were corrected to 20/20. In the Study Cohort, subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: light sensitivity (47.8% vs. 37.2% at baseline) and visual fluctuations (20.0% vs. 13.8% at baseline). In the Control Cohort, the following visual symptoms were reported at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: halos (45.4% vs. 36.6% at baseline) and visual fluctuations (21.9% vs. 18.3% at baseline). Long term risks of wavefront-guided LASIK for myopia with and without astigmatism have not been studied beyond 6 months. Topography-Guided Myopia: The topography-guided myopia clinical study included 249 eyes treated, of which 230 eyes were followed for 12 months. Accountability at 3 months was 99.2%, at 6 months was 98.0%, and at 12 months was 92.4%. Of the 247 eyes that were eligible for the UCVA analysis at the 3-month stability time point, 99.2% were corrected to 20/40 or better, and 92.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "marked" or "severe" at an incidence greater than 5% at 1 month after surgery: dryness (7% vs. 4% at baseline) and light sensitivity (7% vs. 5% at baseline). Visual symptoms continued to improve with time, and none of the visual symptoms were rated as being "marked" or "severe" with an incidence of at least 5% at 3 months or later after surgery. Long term risks of topography-guided LASIK for myopia with and without astigmatism have not been studied beyond 12 months. **Information for Patients:** Prior to undergoing LASIK surgery with a WaveLight® Excimer Laser System, prospective patients must receive a copy of the relevant Patient Information Booklet, and must be informed of the alternatives for correcting their vision, including (but not limited to) eyeglasses, contact lenses, photorefractive keratectomy, and other refractive surgeries. **Attention:** Please refer to a current WaveLight® Excimer Laser System Procedure Manual for a complete listing of the indications, complications, warnings, precautions, and side effects.

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facility (not the surgeon) bills for the drug. Both the facility and the surgeon get to bill for the injection piece.

Q What are the 2023 changes I need to be aware of for ICD-10?

A As noted above, any code changes or guidance goes into effect on October 1, 2022. Our "Eye and Adnexa" in ICD-10-CM (Chapter 7) actually has no new codes or even any code change guidance this time. Other chapters are affected, and your individual practice pattern affects whether you have codes to use or not. The most likely ones affecting eye care are in the Neoplasms (Chapter 2) and the Z codes (Chapter 21).

Q I tried to order ICD-10 books and they won't be available for a while. How can I get something I can show my staff?

A You can access the codes for 2023 at the Medicare CMS.gov ICD-10 site. Once there, you'll notice five downloadable files (four of these are ZIP files containing more than one item). There are two files for you to be especially aware of. The first one is the "FY 2023 ICD-10-CM Coding Guidelines" PDF. Anything in this file with a change from one year to the next is called out in bold, underline or italic typefaces, so it's easy to see the differences for 2023.

The second useful download here is a ZIP folder titled 2023 Addendum. This Addendum folder contains five files. Of these, the most useful file is named "icd10cm_tabular_addenda_2023." This file shows only the new or changed ICD-10 codes for 2023. You may notice Chapter 7 seems to be "missing" in this particular 2023 file. That's to be expected, however, because as noted above, there are no changes. You can also download other files here until you get your books; they're searchable PDF files if you save them electronically.

Q What are the changes to Chapter 2 (Neoplasms)? I sometimes see patients with these conditions and have needed these codes.

A The Tabular Addenda file mentioned above has some new guidance on when to use the primary versus a secondary site condition diagnosis. There's more clarity for 2023 on primary and secondary site designation and when to use each. Some of the conditions you might see a patient for might not be a primary malignancy, so there's been some confusion. The guidance under "Admission/Encounter for treatment of primary site" notes the following:

- "If the malignancy is chiefly responsible for occasioning the patient admission/encounter and treatment is directed at the primary site, designate the primary malignancy as the principal/first-listed diagnosis.
- The only exception to this guideline is if the administration of chemotherapy, immunotherapy or external beam radiation therapy is chiefly responsible for occasioning the admission/encounter. In that case, assign the appropriate Z51.— code as the first-listed or principal diagnosis, and the underlying diagnosis … as a secondary diagnosis."

Under "Admission/Encounter for treatment of secondary site" it states:

"When a patient is admitted because of a primary neoplasm with metastasis, and treatment is directed toward the secondary site only, the secondary neoplasm is designated as the principal diagnosis even though the primary malignancy is still present." This means that if you're involved mostly in treating the secondary neoplasm, use that site as your first diagnosis on claims.

Q What about the Z code changes? I don't use them very often.

A The changes are minor to Chapter 21 (Factors influencing health status and contact with health services) but as payers get more demanding, your use of these might need to increase. If you get payer denials after October 1, 2022, watch the denial codes to see if the payer is actually asking for additional codes as secondary diagnoses before accepting the claim. The small changes here that might affect us in eye care are:

- In the Z59.8 area: "Transportation insecurity," "Financial insecurity," and "Material hardship" have some greater specificity. While not commonly used, some of these might be relevant to some of your patients.
- The Z94.4 (use of insulin), Z79.84 (use of oral hypoglycemic) and Z79.85 (use of injectable non-insulin) codes are all unchanged—but there's a new "Excludes2" instruction for each. CMS has long indicated that Excludes2 notes designate "… that the condition excluded is not part of the condition represented by the code, but a patient may have both conditions at the same time. When an Excludes2 note appears under a code, it's acceptable to use both the code and the excluded code together, when appropriate." This excludes2 note is a clue that both diagnosis codes might not apply to most encounters.
- There are a host of new Z79.6 codes that apply when the patient is on immunomodulators and immunosuppressants.
- There are many new (and more specific) "noncompliance" codes for patients and caregivers in the Z91 area. If they impact the care you deliver, you might consider using them. ◀

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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** are affected by *Demodex* blepharitis (DB).[2,3]

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JEANETTE, real DB patient

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MANAGING THE UPCOMING PROVIDER SHORTAGE

As the number of patients grows and the number of ophthalmologists drops, trouble may lie ahead. Doctors and experts weigh in.

CHRISTOPHER KENT
SENIOR EDITOR

As populations grow, political landscapes shift, technology and expectations evolve and new generations of young people move into the field of medicine, new challenges are slowly but surely arising. One of the many challenges just starting to impact ophthalmologists in America (as well as many other medical professionals) is a steadily increasing supply of patients needing care, with a dwindling supply of surgically trained doctors able to care for them.

Here, doctors and a practice management expert share their experiences and insights about the reasons for this growing problem, and offer a few thoughts about what might be done to address it in a way that serves all patients in need, while maintaining quality of care.

More Patients, Fewer Doctors

"We've known for some time that ophthalmology will be underserved in the future," says John Pinto, president of J. Pinto & Associates, an ophthalmic practice management consulting firm. "This is part of an overall trend in most of the medical specialties, not just in eye care, and it's happening for a number of reasons. Twenty years ago, residency training spots were pretty abundant. Then, because of strictures in government financing, those training slots started to go away. The last time I checked, there had been at least a 10-percent drop in residency training slots in the past decade or two. If you squeeze off the supply line of doctors at the same time as you increase the demand for care, the two things will collide.

"My understanding is that we currently have something like 450 residency graduates every year," he continues. "At the same time, there are something like 550 ophthalmologists retiring every year now, many of them Baby Boomers. If you combine those numbers, in the best-case scenario the number of ophthalmologists is staying even; in the worst case, we're seeing a decline. Looking at the patient numbers, the United States population is increasing about 1 percent a year, while the number of seniors is increasing about 3 percent a year. Seniors use nominally about 10 times as much ophthalmic care as younger patients. So, while the number of ophthalmologists is steady or declining, we're seeing an increase of about 5 percent per year in the demand for care."

Douglas K. Grayson, MD, medical director and chief of glaucoma and cataract surgery at Omni Eye Services in New York and New Jersey, acknowledges that the number of patients seeking eye care is increasing. "Health technology continues to improve and people are more attentive to their health, so they're living longer," he says. "Furthermore, our threshold for doing cataract surgery has gone way down; we're starting to operate on patients with minimal visual complaints. That's increasing the number of patients who are candidates for the surgery."

Frederick W. Fraunfelder MD, MBA, associate dean of faculty affairs, and Roy E. Mason and Elizabeth Patee Mason Distinguished Professor of Ophthalmology at the

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Drs. Grayson and **Fraunfelder** have no financial ties relevant to anything discussed in this article. **Mr. Pinto** can be reached at pintoinc@aol.com.

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One way to increase the number of future ophthalmologists would be to increase the number of residency openings. However, it seems unlikely that the government will agree to do that. Furthermore, some doctors have pointed out that the number of surgical cases available for resident training at academic centers is dropping, making hands-on surgical training potentially inadequate for the number of residents already enrolled.

University of Missouri, agrees that this problem isn't restricted to the field of ophthalmology. "The doctor shortage is a problem throughout the whole health-care system," he points out. "It's most pronounced among primary care physicians in rural areas, but it's true in most specialties in medicine."

Is It Just the Numbers?

Many observing this developing problem believe that it's being confounded by factors that have nothing to do with the number of patients and providers. "A second factor in this equation is that a generation ago, almost all residents would graduate and go off to private practice and work like the dickens," Mr. Pinto notes. "It was a very workaholic age cohort. In contrast, the present generation, God bless 'em, wants a better work/life balance. The up-and-coming doctors don't want to put in a lot of extra hours every week. That's probably a good thing, but it figures into the equation about managing an overload of patients."

"One reason we have a shortage of ophthalmologic care is that so many of the ophthalmologists we train go into practice during their most productive years but then end up working part-time," Dr. Fraunfelder says. "Most of us have seen colleagues do this. It may be that they want to raise a family, need to care for a loved one or have experienced a big change in their life. In some cases, they may have burned out. But the reality is that the government bases its spending on residencies partly on the expectation that the doctors who go through training will be caring for patients full-time. The models don't project scenarios in which many ophthalmologists end up working part-time. I think this is particularly an issue in the field of ophthalmology.

"I feel strongly that the residents we train need to stay in the profession full-time," he continues. "They should feel a responsibility to do so, and we need to instill this in them during their training. Most of their benefits, salary and health insurance are paid for by the taxpayer through CMS. For them to finish their training and then five years later become part-time isn't ethical, unless there's a valid reason for it. I'm convinced that if almost all of our residents practiced full-time we'd have enough coverage to manage all of the patients we expect to see in upcoming years."

"Another issue is physician burnout, a problem seen all across health care, not just in ophthalmology," Dr. Fraunfelder points out. "It's a tremendous problem, and it's a significant loss for our work force when it happens.

"In my experience, ophthalmologists burn out when they focus on things like patient throughput or maximizing efficiency and profits, instead of concentrating on education, service, contributing to the greater good and wearing a lot of diverse hats," he says. "Focusing on maximizing profits is exciting for five or 10 years, but doctors who do that tend to burn out and retire early. We want our ophthalmologists to feel like they have a career, not just a job—something they can still find interesting 20 years into it."

Consequences: Hiring a New Doctor

Not surprisingly, more demand and fewer doctors looking for a position leads to practices struggling to find new hires. "We used to have two doctors for every job opening that was posted," Mr. Pinto points out. "Now we have two jobs for every doctor who's looking. As a result, practices that want to hire a doctor have to wait longer. In a coastal market, it used to take six to 12 months to find a candidate you could hire to be a new general ophthalmologist in your practice. Now it takes 12 to 24 months—sometimes several years—to find a doctor.

"This is exacerbated in rural or secondary markets," he continues. "These are wonderful places to practice because they have an abundant population of patients, but it's problematic to hire doctors because young ophthalmologists typically like an urban, coastal environment. As a result, it can take three years or

more to find an ophthalmologist to join a rural practice. This means that practices looking for a doctor have to plan way ahead of time, and small practices and solo practices in these secondary markets have to live with the fact that they may not be able to find a replacement doctor to bring in to do a succession plan with."

Dr. Grayson notes another factor adding to the hiring challenge. "It's difficult to hire competent administrators and associates because larger entities such as the private equity firms are aggressively hiring both," he says. "That's partly because private equity companies need to replace the older ophthalmologists of the practices they bought. Almost every private equity platform of significance has a full-time recruiter, whereas a private practitioner has to add this recruiting project to his or her busy schedule seeing patients."

Mr. Pinto says that at any given time, about a half-dozen of his clients are in this situation. "They're typically planning to retire in a couple of years, so they look for a replacement doctor," he says. "Many of them eventually realize they're not going to find someone to buy their practice. So, they delay their retirement, or get more creative in other ways, such as merging their practice with another local practice in town. In some cases I've seen practices make a kind of 'Hail Mary pass,' offering exceptionally large starting salaries to try to coax people into these secondary markets. Usually, they aren't able to find a new doctor, so we just close the practice down."

Mr. Pinto points out that this situation is very frustrating for older doctors and private practices trying to bring in an extra doctor, because they have a line of patients out the door needing help. "Such practices are doing all the things you'd expect," he says. "Some are saying they won't be able to grow as much as they'd hoped, and many are digging deep to increase efficiencies. A doctor who preferred to see 30 patients a day ends up seeing 40 or 50 or 60 patients a day to accommodate the market demand, because he or she can't find a new MD or DO to join the practice."

Working With Optometrists

"Many practices are dealing with this problem via labor substitution, which is nothing new," notes Mr. Pinto. "Optometrists have been added to ophthalmology practices for years. If you ask the average general ophthalmologist, the non-subspecialist, what percentage of the visits last week could have been handled by an optometrist, the average answer will be about a third. So optometrists are a really good buffer. Obviously, some ophthalmologists are uncomfortable with that degree of labor substitution, but even if they only let optometrists take over 10 or 15 percent of the practice load, it will help them accommodate the increasing number of patients."

Dr. Grayson favors sharing the workload with optometrists. He believes the way to manage increased patients with fewer providers is to revamp the traditional model of delivering eye care, so that everyone spends most of their time doing the thing they're expert at.

"In some practices a young associate joins the practice and does four to six cataracts a week," he notes. "That's extremely inefficient in terms of the time management, cost

ECONOMIC CONSEQUENCES

John Pinto, president of J. Pinto & Associates, an ophthalmic practice management consulting firm, notes that standard market forces that shape the cost of services and the amount of demand don't necessarily apply in ophthalmology.

"In almost all areas of human commerce, there's a very clear relationship between volume and pricing," he explains. "For example, in the past year and half, house prices have gone up sharply because there was less inventory. The same thing happened with lumber; disruptions affect the price and then the demand. However, in eye care, especially those parts that are third-party funded—and ophthalmology is about 60 percent federally funded through Medicare—the decrease in supply of doctors is not generating a market signal that says, 'Let's go ahead and increase the price.' It's a fixed-price environment. As a result, we may see more practitioners unlinking from Medicare and deciding to become a cash-based practice. Not many ophthalmologists have done that so far, but I predict we'll see more in the future."

Mr. Pinto points out that this doctor/patient ratio shift has impacted the amount young ophthalmologists are getting paid. "Base salaries have been soaring in recent years," he says. "Base salaries for a general ophthalmologist in an urban/suburban area used to fall between $175,000 and $225,000; now they range from $275,000 to $500,000. This increase is especially evident in rural areas, where it's harder to recruit doctors, whether they're new graduates or mid-career doctors looking for a new job."

Mr. Pinto notes that a drop in the number of ophthalmologists could have an impact on private insurance payment rates. "Already, in a market that doesn't have enough ophthalmologists, the ophthalmologists in that market have more pricing power," he points out. "In that situation you may see stronger reimbursement—maybe 110 or 120 percent of Medicare rates. However, this isn't true today in a place like Los Angeles, where there's an abundance of ophthalmologists and the payors have the high ground. They can pay providers at about 80 percent of Medicare allowables. But if there are fewer and fewer ophthalmologists in an area, they should, in theory, be able to drive a harder bargain with the private payor community.

"So far, we're not seeing a lot of that, except in one or two markets here and there," he adds. "But we may see more of that as the labor shortage increases."

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management and overall efficiency. An effective practice model should have surgeons doing mostly surgery, 40 or 50 surgeries at a clip, similar to the LASIK practice model. Preop and postop care should be provided by optometrists. Optometrists are the physician extenders of ophthalmology. That's where I think the future lies.

"America has plenty of optometrists and they're extremely well trained," he continues. "They're currently being trained to be more focused on medical disease and clinical skills, and less on refractions, because refractions are becoming more and more automated. Their focus is shifting in ways that make them better suited to act as physician support in ophthalmology practices.

"At the same time, ophthalmologists should be focused on doing what they're good at," he says. "Retina specialists shouldn't be spending all of their time giving injections—that's an inefficient use of their skills. Their time should be spent fixing detachments, doing vitrectomies, analyzing fluoresceins. Progressive retina practices have physician assistants or other alternatives, like a retired ophthalmologist, to handle the injections. I don't think we need more retina specialists—we need them to be spending their time on things that only they can do.

"The same is true for glaucoma specialists," he continues. "Does a glaucoma specialist need to manage an office filled with 75 patients who are stable on their drops? Those doctors should be managing surgery and addressing patients who are complex or are failing despite maximum medical treatment. Clearly, you have to have ophthalmologists in the office to deal with more complicated cases involving glaucoma, cornea or retina, but if we migrated to a model like the one I'm describing, there wouldn't be a provider shortage."

Douglas K. Grayson, MD

Many practices are hiring multiple optometrists and using division of labor to help the practice manage an ever-increasing number of patients.

Dr. Fraunfelder also sees engaging with optometry colleagues as a promising way to help manage the provider shortage. "We have a tremendous opportunity to work with them in primary eye care, nonsurgical eye care and rural eye care," he notes. "Our optometry colleagues are eager and quite capable of working with us. They go to four years of college and major in science; then they go to four years of optometry school, so they're highly trained. They can take care of common eye disease, and we shouldn't feel threatened by that. It makes sense to collaborate with them. I know not everyone likes the idea, but I think it's an important part of the solution."

The Scope-of-Practice Debate

Of course, the tasks that can be managed by an optometrist are dependent, in part, on state laws governing scope of practice. "Selected states are liberalizing scope of practice for optometrists," Mr. Pinto observes. "Eventually, it's likely that incisional care will be granted to optometrists in some states. Obviously this is very controversial, but some ophthalmologists will probably find it acceptable and helpful for managing the patient crunch. Others, of course, will be horrified. Many ophthalmologists are still upset about optometrists being allowed to prescribe therapeutics."

Dr. Fraunfelder does have serious reservations about optometrists performing any type of surgical procedure. "Our most sophisticated technical school is medical school, and the highest level of competence arises from getting into medical school, completing medical school and doing post-medical-school training, such as residency, fellowships and internships," he says. "I think our country wants our surgeons to have gone through that. I have a tremendous amount of respect for optometry and optometry education, but surgical interventions should be reserved for doctors who've gone through medical school and done the training that's required. Doctors should educate themselves, not legislate themselves."

"Partnership with optometry is extremely important from a population health perspective," says a spokesperson for the American Academy of Ophthalmology. "However, this means a rational division of labor. High-risk, high-intensity diagnostic and interventional tasks should be assigned to ophthalmologists whose training specifically addresses these areas. What doesn't serve the population well is for the quantity of care to go up and the quality to go down. Our policy and advocacy teams are deeply engaged in the process of establishing and maintaining that balance as we also strive to forge partnerships."

Dr. Fraunfelder believes that disagreements about scope of practice would be much less common if optometrists were more involved in

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PRIVATE EQUITY AND THE PROVIDER SHORTAGE

Private equity firms, which have purchased a significant portion of ophthalmology practices in the United States, have become a major factor influencing how the field of ophthalmology functions, and how it may function in the future. How might they influence (or be influenced by) a provider shortage?

John Pinto, president of J. Pinto & Associates, an ophthalmic practice management consulting firm, points out the supply and demand situation of fewer doctors and increased demand is actually not working to the benefit of private equity companies. "The reality is that in this market, private-equity-owned practices are competing with private practices that can afford to pay their associates and partners more," he explains. "Let's say you have a practice that has $1 million in collections and a 40-percent profit margin. If that was an independent practice, the doctor/owner would take home $400,000 a year. But if that same practice is transferred into a private equity context, part of those earnings are retained by the private equity company as a way of paying back their investment. The typical division of the profits, in that example, would have about $100,000 going to the private equity company and $300,000 going to the doctor.

"That's fine if the doctor is 68 years old and has gotten the multi-million-dollar payout from the private equity company," he continues. "However, it's not so great if the private equity company needs to replace that older doctor and all they can offer is the $300,000 that the practice has available for provider compensation. The private practice that's in the market to hire that same young doctor looking for a job can offer a higher salary—a full measure of private practice profits.

"We often represent young doctors looking for positions, helping them negotiate salaries and terms, and we're beginning to see these clients getting offers from private practices that are 10 or 20 percent greater than the offers from private equity companies," he says. "I think this is going to put a real squeeze on the private equity segment of this industry."

Mr. Pinto notes that he saw this coming years ago. "Even 10 years ago it was easy to see that it was eventually going to get harder to hire doctors, and that this might knock a lot of private equity firms for a loop," he says. "It's going to be tough for these companies. There will be a lot of doctors buying back their assets for salvage value before this is all over."

Nevertheless, Douglas K. Grayson, MD, medical director and chief of glaucoma and cataract surgery at Omni Eye Services in New York and New Jersey, believes that, on the whole, private equity will be good for the field of ophthalmology in terms of managing an increasing number of patients. "The reason is economy of scale," he explains. "Private equity companies are able to consolidate practices, centralize human resources, centralize billing, centralize computer systems and then have full-time people maintain those computer systems. This takes a tremendous burden off the doctors.

"Of course, the private equity companies are in this for profit, but ultimately they know they can't control medical decision-making," he notes. "They don't ever want to be accused of compromising patient care. They don't want somebody pointing the finger at them and saying, 'Look, you're making us see 25 patients an hour, and that's not good for patients.' Meanwhile, the relationship is good in terms of expanding potential for building ASCs, hiring more doctors and hiring more support staff. That reality should help practices manage the increasing number of patients."

—CK

medical schools. "Today, optometry schools are separate, so optometrists don't train in our centers," he notes. "Nevertheless, we do have optometrists in our academic centers. They play a role, especially in the areas of eyeglasses and contact lenses.

"I think if we made optometry a division within our academic centers, we wouldn't have so many conflicts about scope of practice," he says. "If optometrists were trained in our academic eye departments, they'd see what an ophthalmology resident goes through to get to that level of training. We'd understand each other better. Why not have the optometry division of our department also train optometry students? I know of academic departments that already do that."

The "Optometry Model" In Action

"We've been using an optometry-friendly model since the beginning of my practice," Dr. Grayson says. "We've always believed in sharing our patients with a team of optometrists. I wouldn't call it co-management, because that implies that the optometrist is outside of the practice; this is optometry internal to the ophthalmology practice. They see our preop patients, make diagnoses and see postop patients. In our practice model, the ophthalmologist actually has minimal interaction with patients, aside from meeting them and saying, 'Hi, do you have any questions? Let's go do your cataract.' Again, it's somewhat like the LASIK practice model."

Dr. Grayson says his doctors primarily spend their time doing the things only they can do. "For example, our optometrists manage many of our glaucoma patients," he says. "If a glaucoma patient needs a laser, they're sent to me. If the patient reaches a point at which our optometrist feels medical management and laser has failed, then the patient goes on my schedule. I see the patient and we have a surgical consult. That's using the area of my expertise.

"The other advantage of this system is that doing what we're most qualified to do all the time helps us become expert at it and remain so," he points out. "Our pediatric specialist mostly just sees patients who need surgery. He can do 30 cases in


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References: 1. Clareon® PanOptix® Trifocal Hydrophobic Acrylic IOL Model: CNWTT0 DFU. 2. Lehmann R, Maxwell A, Lubeck DM, Fong R, Walters TR, Fakadej A. Effectiveness and Safety of the Clareon® Monofocal Intraocular Lens: Outcomes from a 12-Month Single-Arm Clinical Study in a Large Sample. Clin Ophthalmol. 2021;15:1647-1657. Published 2021 Apr 20.
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a row and do them well. If he only did one case a month and spent the rest of his time measuring kids' vision, he wouldn't be as good at the surgery."

Dr. Grayson notes that the younger ophthalmologists joining the field are less willing to put in extra hours, but says his practice model results in that factor not undermining the amount of care the practice can provide. "The young doctors come in expecting to have help from techs and optometrists," he notes. "They expect to show up at 9:00 a.m. and leave at 5:00 p.m. It's a feeling of entitlement that I don't think is justified, but on the flip side, the kind of practice we've created makes that workable—even for me. Having a huge optometry support staff and techs, I can go in, see 100 patients, then go to the OR and do 60 cases, and still be done at a reasonable hour.

"We have one associate who always leaves at 5:00 and goes home at noon on Fridays, but she's doing 1,600 cases per year," Dr. Grayson adds. "That's possible because of the system and support team we have. Those numbers were unheard of in most practices 25 years ago, but to her it's an average day. It's annoying to see associates come in and act as if this was expected, but this system does make them more efficient."

Dr. Grayson notes that for this practice model to work, egos have to be set aside. "If you decide that you're the only one qualified to do many of these chores, you're going to have a hard time managing more and more patients," he says. "And with automation handling so many of the measurements today, we don't need to personally take them. I used to have to look at a patient's macula to see if there was an epiretinal membrane before doing cataract surgery, because I didn't want the patient to have a subpar result. Now an optometrist shows me the OCT; if I see an ERM I proceed accordingly."

Dr. Grayson says this practice model works very well. "I think this is where the future of ophthalmology lies, although it may take a while for the field to get there," he says. "When I first spoke about this model years ago, I got hate mail! Today, bringing in optometrists is much more widely accepted. Besides, ophthalmologists coming out of training today are more open-minded and understanding about integrating with optometry. These young ophthalmologists expect more support services, whatever kind of practice they go into.

"The bottom line is that our practice model delivers patient care at a level that's way beyond what most general ophthalmologists can offer," Dr. Grayson concludes. "My optometrists see the patients first, and they're top-notch. We don't miss stuff. I'm proud of our model. I think we do a great job."

Create More Residency Slots?

Another way to address the shifting doctor-patient ratio would be to train more ophthalmologists. This would require creating more residency training slots, however, and that could be easier said than done.

"Ophthalmology residency spots have always been sought after," Mr. Pinto notes. "It's a great specialty that has a lot going for it—lifestyle, economics, intellectual fascination and more. I can't imagine that there's ever been an ophthalmology residency program in America that had trouble filling all of their available slots. So one way to improve the imbalance between providers and patients would be to get more federal funding to open up more standard residency slots."

"Increasing the number of residency slots is a potential solution to the provider shortage," agrees Dr. Fraunfelder. "However, I doubt that CMS is going to increase spending on ophthalmology. In fact, they're targeting ophthalmology for decreased spending. So they're probably not going to let us have more residency slots."

Dr. Grayson believes increasing residency slots wouldn't be the best solution to this problem in any case. "We don't need more residency training," he says. "In fact, if you try to train more residents, you're doing them a disservice, because they can't be trained as well today. It's not that the instruction is inadequate, it's a lack of hands-on case experience.

"Medicare and Medicaid insurance changes have limited the advantages of having your cataract done by

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a resident in a hospital eye clinic, versus going to a large practice," he explains. "As a result, there's been a decline in patients going to clinics, which means residents don't get to do as many cases during their training. I can see the difference in the new residents coming out. They may know more about phaco surgery than we did at that point in our careers, but they don't necessarily know what to do when things go wrong; they haven't had the breadth of experience in their training.

"In this climate we still need academic centers to manage the special, unusual cases, but not for routine care," he says. "So I don't think we should be opening up new residency slots and training more people. We don't need to train more ophthalmologists. We just have to better utilize the ones we've got."

"The sum total of the workforce is a combination of people coming in and people going out," a spokesperson for the American Academy of Ophthalmology adds. "Residency programs are limited by the graduate medical education spots made available to them by Medicare. While residency funding has increased recently—targeted to underserved areas and regions with newly established hospital training programs—hospitals infrequently consider assigning spots to ophthalmology. That's a problem. On the other side of the equation—people coming out of these programs—sustainable reimbursement is a high priority if skilled individuals are going to be retained. Both issues point to the need for rational federal support through Medicare. Our advocacy team is intensely focused on Medicare payment reform."

Other Possible Solutions

A few other possible ways to address the provider shortage are worth mentioning:

• ***Allow more foreign ophthalmologists to immigrate.*** "One solution to the doctor shortage would be to liberalize foreign medical graduate admission to the country," Mr. Pinto notes. "There are plenty of offshore ophthalmologists who are well-trained, who would be a great addition to the profession in America. However, our laws make that quite challenging.

> **An individual doctor can't change the macro factors that are causing this problem. He or she can hire optometrists or choose to work harder themselves. But the options for action are limited. The reduction in training slots, for example, is a problem for the federal government to solve.**
>
> ***—John Pinto***

"This is not my area of expertise, but my understanding is that even for countries with whom we have a close relationship, democracies that have great educational systems, vetting protocols and the rest, it's tough," he says. "In order to become an ophthalmologist over here, you not only have to jump through the hoops required to change your citizenship, you have to repeat a significant amount of your training.

"Obviously, some people actually do this," he adds, "but it's quite a challenge. Unless the regulations are liberalized, it will continue to be difficult to see foreign medical graduates as a good solution to this problem."

"This is mostly out of our control," notes Dr. Fraunfelder. "We aren't policy makers for the government, and we don't control who gets visas. Most of the waivers that occur at the government level are given for primary care physicians, not ophthalmologists. So it's difficult to get eye-care specialists here from other countries, even though they're very well trained. They have to take additional tests and jump through a lot more hoops than U.S. graduates."

• ***Allow private-practice-based residencies.*** "Currently, an ophthalmology residency training slot has to be tied to a university-affiliated program," Mr. Pinto notes. "That's not the case for fellowship. If you want to do a plastics fellowship and you already have a residency in ophthalmology, you can go to Mike's ophthalmology clinic and get training from Mike for a couple of years and be able to call yourself a fellow of a plastic fellowship program, with varying degrees of formality. So one possible way to compensate for the limited number of traditional residency spots would be to allow private-practice-based residencies. A doctor might bring someone into the practice who's graduated from medical school and finished their internship, and then spend three years teaching them to be an ophthalmologist.

"Certainly, some large practices might like to get into that activity," he notes. "Such an arrangement would create a stock of future doctors for their own clinic, while also giving the practice extra hands during the training period."

However, Dr. Fraunfelder has reservations about having students do residency outside of a medical school environment. "I'd prefer that our residents learn in a culture of research, discovery and education, which they're most likely to find here," he says. "We cultivate faculty who are good teachers and good clinicians and surgeons, individuals who are highly motivated to teach and to be around learners. Many of the opinion leaders, scientists, doctors with grants, doctors with publications and doctors who are the editors of journals are in the academic health centers. You want your trainees to be in that environment.

"I don't think it's a good idea to be trained in a practice where there may

be more of a focus on the business of ophthalmology," he adds. "That's important, of course, but it's just one part of what doctors in training need to learn. I'd hate for trainees to lose sight of how important it is to be an expert in the science of ophthalmology and the art of patient care. I think they're more likely to get the training they need in this kind of academic environment."

• ***Medical tourism.*** "Another option for dealing with excess patients would be sending some of them out of the United States," Mr. Pinto points out. "We see this to some extent in reverse—some Canadians come to northern U.S. states for cataract surgery, to avoid the wait for government-paid surgery at home. However, I think that sending patients out of the U.S. might not happen until the imbalance grows severe, when we really have people waiting long intervals to get appointments for care. That might be pretty far down the line."

Making the Best of It

Mr. Pinto points out that only so much of this changing doctor-patient ratio is under the profession's control. "An individual doctor can't change the macro factors that are causing this problem," he says. "He or she can hire optometrists or choose to work harder themselves. But the options for action are limited. The reduction in training slots, for example, is a problem for the federal government to solve."

"Population growth and aging doesn't happen in a vacuum," notes a spokesperson for the American Academy of Ophthalmology. "Technology changes that can enhance the productivity of physicians also occur. In partnership with a number of academic institutions across the country, the AAO is actively engaged in research aimed at developing clinically relevant tools to enhance quality, efficiency and cost. Furthermore, there will be an increasingly important role for well-trained supporting personnel, including medical assistants, technicians, orthoptists and so on. The Academy is committed to enhancing our educational and professional development support for these important team members."

"Philosophers have pointed out that some problems can be solved, while others are things we simply have to live with," Mr. Pinto concludes. "The growing gap between the number of ophthalmologists and the number of patients needing care could turn out—at least in part—to be one of those things we'll just have to live with." ◀

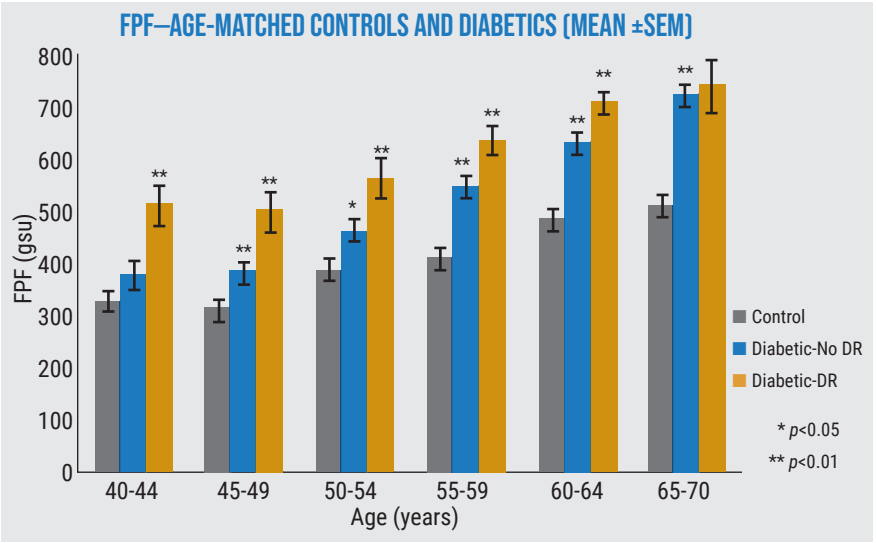
(Continued from p. 8)

New Tech for Glaucoma

is sensitive to? Those are questions we don't have the answers to yet."

Dr. Rosen says several investigators have already expressed interest in participating in further testing. "This device is currently in a number of centers, including Stanford University and the Cole Eye Institute," he says. "We're having conversations with different glaucoma groups around the country about doing studies. Of course, seeing how this plays out in the clinical sphere will take a lot of work, in terms of enrolling patients who are well-characterized with different levels of glaucoma. Right now, we just have proof of concept. A lot of things get to this stage and look very promising, but in the end, it's hard to tell whether they'll actually make it to the ophthalmologist's lane."

Dr. Rosen notes that even if this measure turns out to be more sensitive than visual fields, it could take a while to fall into common usage. "People are comfortable with what they know, so it would probably start out as a supplement to visual fields and OCT. But if it continues to produce these kinds of results, I believe the future of this technology is bright." ◀



In this study, the levels of flavoprotein fluorescence were significantly higher in most diabetic eyes than healthy eyes—and even higher in diabetic eyes with diabetic retinopathy—in every age group. *(Unpublished data from Matthew G. Field, MD, Victor M. Elner, MD, PhD, and Donald G. Puro, MD, PhD.)*

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CURRENT DIAGNOSIS AND MANAGEMENT OF UVEITIS

A retina specialist walks you through the treatment options for this sometimes confounding condition.

SRUTHI AREPALLI, MD
NASHVILLE

Uveitis can be a challenging condition to manage, with a dizzying array of treatment options. These options have varying degrees of efficacy, selection criteria for use, as well as different side effects that also must be taken into account when you're choosing a treatment path. Here, I'll review our current options for quelling uveitis and avoiding medication side effects as best we can.

Diagnosing Uveitis

Uveitis is traditionally defined as the inflammation of the uveal structures, which include the iris, ciliary body and/or choroid.[1] The site of involvement, such as anterior, intermediate, posterior or panuveitis, categorizes the disease.[2] Untreated, uveitis can cause visual decline through many mechanisms, including, but not limited to, macular edema, optic nerve edema and cataract.[3] All new uveitis patients, and follow-up patients not responding as expected, should be dilated to best categorize their site of involvement, as this can formulate a more precise diagnosis (*Figure 1*).

The diagnosis and management of uveitis can be tricky for multiple reasons: The disease has variable presentations, and patients sometimes provide an incomplete history or are difficult to examine (particularly children). In addition, uveitis is fraught with visually threatening complications and/or systemic manifestations. Despite all this, with the correct diagnostic approach, a concise differential can be reached, and thankfully, multiple treatments exist to quell inflammation. When choosing a therapeutic agent, it's essential to balance the ability of these drugs to induce disease remission against their potential side effects and toxicities.

This review will focus on intermediate, posterior and panuveitis treatment, which have a combined prevalence of 23 per 100,000 adults, and are even less common in children.[4] When approaching treatment, it's important to understand the underlying cause, as this will direct your treatment algorithm. The manifestations of uveitis are either primary, where the eye is the only site of known involvement, or secondary to a systemic immune or infectious condition. In terms of systemic conditions, infectious disease is much more common in developing countries (with rates as high as 50 percent of all cases), while non-infectious causes are the most common causes of uveitis in more developed areas.[4] When working up a patient with uveitis, the three most common diagnoses I consider and/or want to rule out for treatment considerations are sarcoidosis, syphilis and tuberculosis, but my differential is tailored extensively after taking into consideration the patient's medical history and exposures. In any case of suspected infection, perform an aqueous or vitreous tap before administering steroids, especially before administering local or periocular deposits.

As a side note, in children, disease can be especially difficult to recognize and treat, and in certain cases an examination under anesthesia can be necessary if an outpatient examination is low-yield. Recognizing uveitis is difficult in these patients, as they can be asymptomatic or have

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Dr. Arepalli is an assistant professor in the Vitreoretinal and Uveitis Service at Emory University.

more chronic disease, and/or they may not be able to verbalize their issues at all.[5] Moreover, visual complications result in amblyopia in at-risk age groups, with long-lasting social and economic ramifications. In these situations, I recommend consulting with a uveitis specialist for evaluation and management early on. I also advise a careful examination in cases of trauma-related uveitis, particularly in children, to rule out cases of globe rupture or retained foreign body (*Figure 2*).

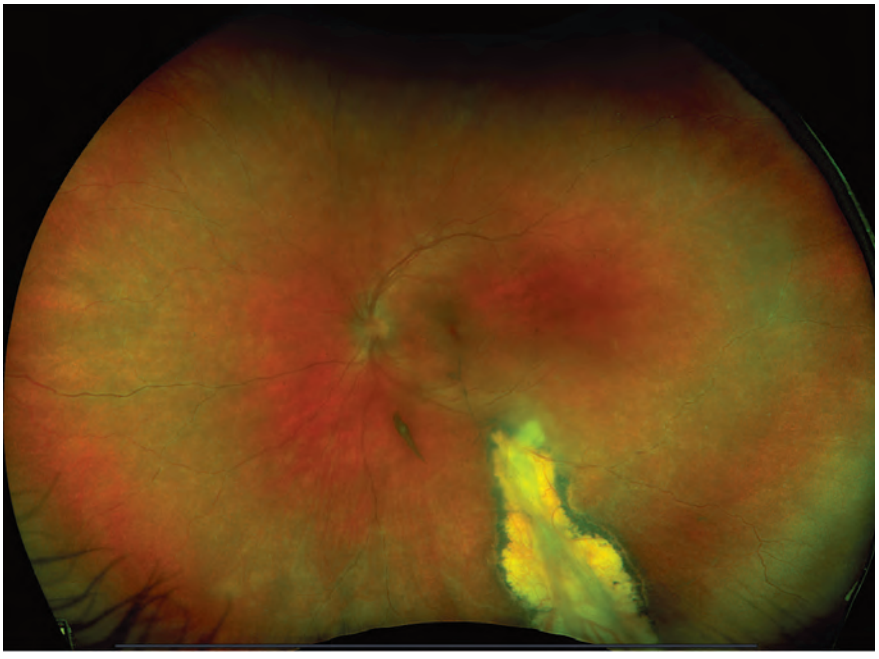

Figure 1. A 17-year-old female sent in for evaluation for presumed anterior uveitis. Dilation showed intermediate and posterior involvement with a large chorioretinal scar consistent with toxoplasmosis. There's an area of re-activation at the posterior edge of the lesion as well as vascular sheathing.

Treatment

Treatment aims at obtaining quiescence of the disease, either by treating the infectious agent or treating the immune condition. Remember, in cases of suspected immune disease that don't improve or even worsen with steroids or immunosuppression, consider the possibility of infection or malignancy.

Following are the treatments at your disposal:

Corticosteroids

The initial therapy for uveitis is often corticosteroids, which can act quickly to quiet inflammation. Briefly, their mechanism of action relies on their ability to bind to receptors within cells involved in the inflammatory cascade, ultimately leading to the downregulation of pro-inflammatory molecules and cytokines.[3] Given their widespread effect at dampening inflammation, they're instrumental, but I remind patients that they're often not an ideal long-term option.

As you know, steroids come in various levels of intensity. In new patients, or patients for whom their diagnosis isn't clear, I prefer to stick to methods that I can quickly stop or change. In these patients, when the inflammation is mild, I often stick with topical therapies while completing their work-up, in case an infectious cause is found. However, in cases of advanced intermediate, posterior, or panuveitis, I'll dispense a small amount of oral steroids, emphasizing to the patient the importance of adherence to the drug regimen, and I'll order lab work so I can monitor their response to the treatment and complete their work-up. I don't administer local steroids (like posterior sub-Tenon's Kenalog or intravitreal steroids) until I'm sure I've ruled out infection. In cases of recurrent or recalcitrant inflammation, I start the discussion of steroid-sparing therapy early.[3]

Topical steroids, such as prednisolone acetate 1% or difluprednate 0.05%, have good effects on anterior uveitis, but I'll also use them in mild cases of more posterior-involving uveitis. I upgrade to difluprednate if there's more posterior inflammation or macular edema, as it's been shown to have higher rates of vitreous penetration than prednisolone, keeping in mind that this is a higher strength topical steroid and carefully monitoring for steroid issues, such as cataract and glaucoma.[6,7] I have a low threshold for increasing treatment to oral or local therapies once infection is ruled out, as undertreatment of uveitis is linked to worse visual outcomes. If the patient has anterior chamber cell or is forming posterior syenchiae, I'll also start dilating drops to prevent or break up the synechiae, and keep track of the formation of synechiae in case they progress to iris bombe and require a laser peripheral iridotomy. Topical therapies are also useful in testing a patient's steroid response, which can be kept in mind when considering local steroid therapies. Punctal occlusion can help reduce any systemic exposure of the drugs.

In patients with more extensive uveitis, oral prednisone is most commonly used, with the dose ranging between 1 to 1.5 milligrams/kilogram, but, given the side effects, I rarely dose patients above 80 mg even if their weight would dictate a higher amount. I move towards oral therapy quickly when patients have issues that also require quicker intervention, especially when there's foveal-adjacent pathology or they're

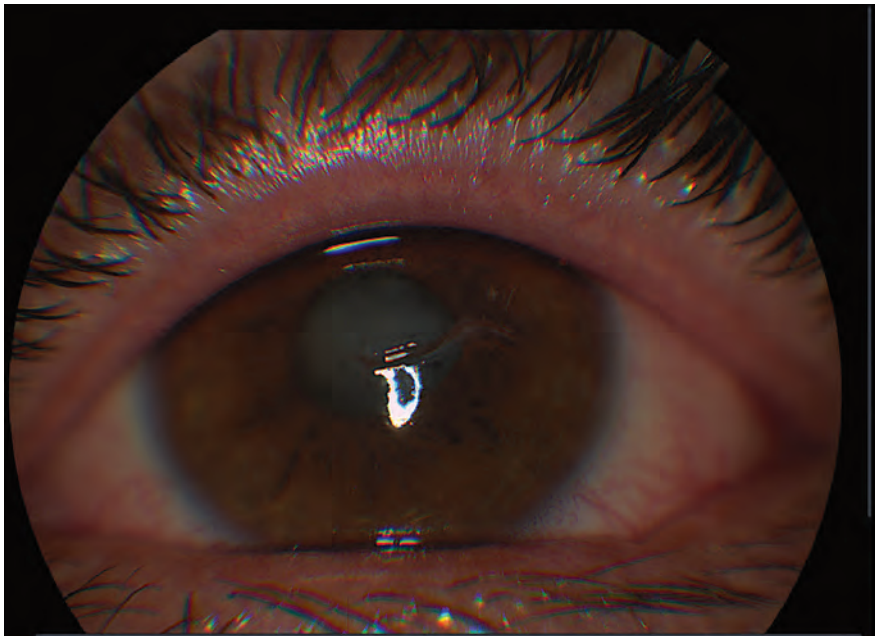

Figure 2. A 23-year-old male sent for assessment for traumatic iritis with a difficult examination at the slit lamp. Careful ocular evaluation revealed a full thickness corneal laceration, iris plugging of the wound, iris peaking and evidence of early endophthalmitis; orbital imaging showed a retained metallic foreign body.

monocular. When starting oral steroids, I keep in mind my endpoints for steroid treatment, so when they're reached I can begin tapering the medication. The rationale for this is twofold: a tapering schedule should be followed after two weeks of high-dose oral steroids instead of abruptly stopping them, as this has been linked to adrenal insufficiency. Additionally, I try to get patients off of oral steroids within a reasonable time frame, since they have a multitude of side effects, including decreased bone density; peptic ulcers; Cushing syndrome; blood sugar and blood pressure deregulation; weight gain; immunosuppression; and mood deregulation.[8] The literature has shown that a maintenance dose of 7.5 mg daily or less has the least systemic side effects and I work towards this with patients, but would ideally like them off steroids in the long term.[3] Oral steroids are generally considered safe in pregnancy, but there have been reports of steroid use being linked to cleft palate in the fetus, particularly with use during the first trimester, though this is debated.[9] In children, I'm especially cognizant of the amount and length of steroid use as this can lead to osteonecrosis.

In rare cases, I'll initiate intravenous corticosteroids with careful serial ocular examinations and after I've ruled out infection, especially in patients with severe inflammation, foveal-threatening lesions, optic nerve involvement or monocular status. An IV pulse of methylprednisone (1 gram daily, for three days), with plans to transition to an oral regimen is my usual approach.

A myriad of options exist for local therapy, including periocular depots, intravitreal injections and implants, surgical implants and suprachoroidal administration. The advantages of local therapy include avoiding systemic side effects as well as a more direct administration of therapy. However, some of the general disadvantages of local therapy include cataract, steroid induced glaucoma and difficulty in removing the steroid if necessary. As stated prior, I always rule out infection before administering local steroid.

Periocular therapy, usually consisting of triamcinolone acetonide 40 mg/ml can be injected into the sub-conjunctival space (usually in cases of anterior scleritis), and in cases of more posterior involvement, trans-septally or in the sub-Tenon's space.[3] Typically, a 27-gauge needle is used to administer 40 mg/ml of triamcinolone acetonide; if performing a trans-septal injection an inferior approach is usually taken, while a sub-Tenon's injection can either be superotemporal or inferior. When engaging the trans-septal or sub-Tenon's space, I aim posterior to the equator and move the needle laterally and medially to make sure I haven't engaged the globe itself, as this can lead to retinal tears, detachment, and administration of steroid intra-ocularly. Both injections are associated with cosmetic complications: the inferior administration of trans-septal steroid can cause fat prolapse, and superior sub-Tenon's injection can cause injury to the levator palpebrae, resulting in ptosis.

Intravitreal injections provide another avenue of steroid implementation, particularly in patients who can't tolerate steroids or other immunosuppressive therapies, those who fail periocular administration, don't respond enough to oral steroids, or have immediate, vision threatening pathology.[10] Whenever I administer an intravitreal steroid, I prefer to use of 2 to 4 mg of preservative-free triamcinolone acetonide. The disadvantage of this medication, though, is its relatively short duration, (usually three months, but it can last slightly longer), requiring frequent re-administrations.[11] In certain patients that demonstrate a favorable response to intravitreal triamcinolone, I follow that bolus with an intravitreal implant to gain longer lasting effects.

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Discover continuous calm in uveitis[1]

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

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

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

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

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

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

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

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

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

EYEPOINT® PHARMACEUTICALS

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

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

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

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

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

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

6. ADVERSE REACTIONS. 6.1. Clinical Studies Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

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

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

(continued)

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

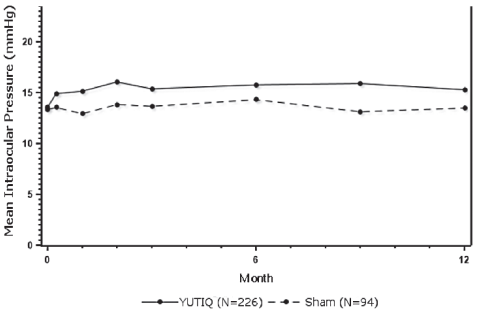
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

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

Table 2: Summary of Elevated IOP Related Adverse Reactions

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

Figure 1: Mean IOP During the Studies



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

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

implant (Yutiq, EyePoint Pharmaceuticals).

The Ozurdex implant is a completely biodegradable dexamethasone implant with a lactic-acid glycolic matrix; this matrix is what leads to corneal degradation in the cases where the implant migrates into the anterior chamber. The injector is 22 gauge, and I often used a beveled incision when delivering the drug, much like inserting a trocar for vitrectomy. The medication may last for up to six months, but often peaks at two months, with a small residual effect lasting for up to three to four months after injection.[12]

The Yutiq implant is a non-biodegradable implant composed of a polyamide cylinder with internal steroid that delivers a slow, low-rate release of steroid over three years.[13] Compared to Ozurdex, this theoretically could provide a patient with fewer injections and long-lasting control, but in patients with profound inflammation, Yutiq may not provide enough coverage. I also find the Yutiq implant useful in cases of post-cataract driven inflammation and macular edema, as the inflammation in these cases is usually mild. The disadvantages of Yutiq include a possibility of anterior chamber migration, and the accumulation of multiple Yutiq devices with repeated injections.

When debating the type of local treatment, I often consider the results of the POINT study, which compared the use of Ozurdex versus intravitreal triamcinolone versus sub-Tenon's triamcinolone; all groups showed a significant improvement in visual acuity and central retinal thickness; however, the intravitreal groups showed a significant difference in the reduction of central retinal thickness and improvement in visual acuity compared to the sub-Tenon's group. The intravitreal patients had a higher rate of intraocular pressure rise, and because of this, in patients with a history of steroid response, I tend to stay with more periocular administrations if local steroid therapy is necessary.

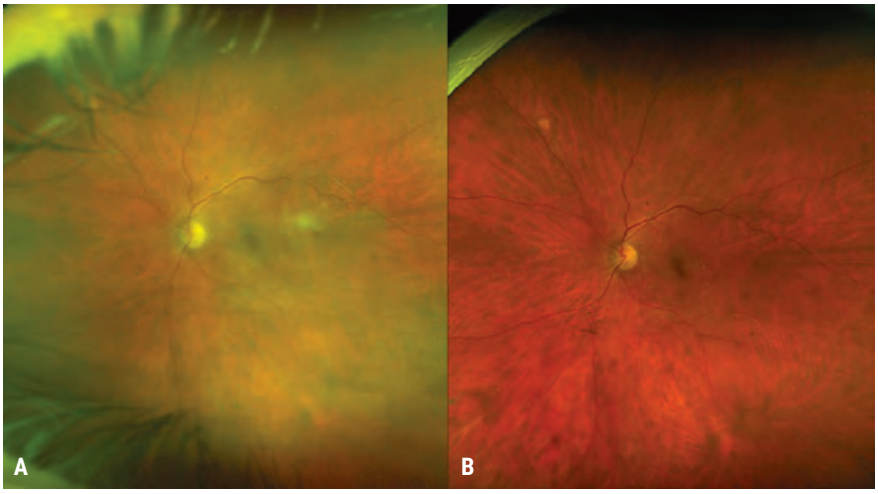


Figure 3. A 59-year-old female presenting with bilateral intermediate uveitis (A) that required 60 mg of oral steroids with an appropriate taper after infectious etiologies were ruled out (B).

The use of the suprachoroidal space has become more popular in drug development, and recently gave rise to the approval of Xipere (triamcinolone acetonide injectable suspension, Bausch + Lomb/Clearside Biomedical) 4 mg/0.1 ml.[14] Xipere is administered into the suprachoroidal space with a microneedle that comes in two sizes. This is advantageous in patients with mostly posterior pathology, and theoretically has a lesser risk of developing cataract or steroid response pressure rises in patients due to the posterior depot of the medication.[14] Additionally, I consider this medication in patients without an intact lens barrier, or those who are aphakic, as I would be concerned about drug migration with an intravitreal administration. The disadvantages of this medication are that there can potentially be inadvertent entry into the globe resulting in retinal detachment or tears, as well as choroidal pathology.[14]

A surgical implant also exists for the treatment of intermediate, posterior and panuveitis; a 0.59 mg flucinolone implant (Retisert, Bausch + Lomb), which is sutured to the sclera and lasts for up to three years, if not longer.[15] The Multicenter Uveitis Steroid Treatment Trial showed increased control with the Retisert implant compared to systemic therapy in uveitic eyes (88 percent vs. 71 percent) and equal visual acuity at 24 months. At seven years, however, the visual acuity was better in the systemically treated group.[16] The disadvantages of this therapy include a large bolus of steroid that increases the risk of cataract, steroid-related pressure increases, intraocular bleeding, and hypotony with poor wound closure, and results in the loss of scleral and conjunctival real estate that would have been useful for other ocular procedures down the line, especially if multiple implants are needed.

Steroid-sparing Therapies

In patients whose inflammation is recurrent or whose steroids can't successfully be tapered down to appropriate maintenance dosing, or who are experiencing complications with local or systemic steroid therapy, steroid-sparing treatments are an excellent option. Treatment options in this class include antimetabolites, biologics and alkylating agents.

• ***Antimetabolites.*** Methotrexate, a folic acid analog, is often used in both adults and children given its

well-researched safety and efficacy profile.[17] It can be administered subcutaneously or orally, and dosages typically range from 10 to 25 mg. I prescribe this with a daily folic acid to help curb some of the side effects of the medication, which include oral ulcers, gastrointestinal discomfort and hair loss. Serious clinical and lab manifestations include interstitial pneumonitis, alterations in liver function tests and bone marrow suppression.[17] In order to monitor patients, baseline labs should be obtained, and routine lab work should be done every three months.

Azathioprine and mycophenolate mofetil are two other antimetabolites, both of which inhibit purine synthesis, in turn blocking the maturation of lymphocytes. Azathioprine is dosed at 1-3 mg/kg/day, while mycophenolate is administered at a maximum of 1,500 mg twice a day. The most common side effects include gastrointestinal distress, but serious complications can also arise, including bone marrow suppression. Thus, like methotrexate, baseline labs as well as lab work every three months should be done to monitor for these. Of these antimetabolites, only azathioprine is safe in pregnancy. Anti-metabolites should generally not be combined with another anti-metabolite, however they can be used in combination with other forms of steroid sparing drugs, such as anti-TNF-α medications.

• ***Biologics.*** TNF-α inhibitors are mainstays of the biologic class of drugs. These medications target TNF-α; a potent cytokine in the inflammatory pathway, and are generally well-tolerated in both adults and children. In cases where a patient can't tolerate anti-metabolites, or needs to be transitioned quickly to a steroid-sparing agent, I'll often consider an anti-TNF-α medication. The biologic adalimumab is a fully humanized anti-TNF- α monoclonal antibody, which has been shown to be effective in intermediate, posterior and panuveitis, as well as in children with JIA.[18-20] Dosage of adalimumab is typically 40 mg, administered subcutaneously, every other week, but in certain patients, it can be used on a weekly basis. Another biologic agent is infliximab, a chimeric monoclonal antibody with proven results against posterior uveitis in both children and adults, often dosed between 5 mg/kg and 10 mg/kg via infusion.

Other agents in this class include etanercept, golimumab, and certolizumab; with the last two having modest amounts of literature supporting their use in uveitis. Conflicting evidence exists regarding anti TNF- α medications in pregnancy, but they're generally considered safe in early phases of gestation.

There's also rituximab, a monoclonal antibody focused against CD20; and tocilizumab, a recombinant monoclonal antibody targeting IL-6, intravenous immunoglobulin or interferon. Tocilizumab has proven particularly promising in reducing vascular leakage and macular edema.

Alkylating agents

Rarely, alkylating agents, such as cyclophosphamide and chlorambucil, may be used for severe, refractory cases of uveitis, but their toxicity profile is large and robust. When initiating treatment in women of childbearing age, always consult with rheumatology and OB/GYN before starting immunosuppression, and confirm the lack of pregnancy.

In conclusion, a myriad of therapeutic options exists for intermediate, posterior and panuveitis patients. Typically, the algorithm consists of ruling out infectious etiologies, starting with corticosteroids and—if unable to taper down the steroid or obtain adequate control—the addition of steroid-sparing therapies. ◀

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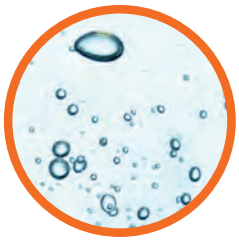

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- **Extra Long-Lasting Hydration**[1-8]
- **Locks in Moisture**[5-8]

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POINT:
KERATOCONUS IS PRIMARILY A REPETITIVE STRESS INJURY

EYE-RUBBING IS KEY TO PROGRESSION

While keratoconus likely has multiple causes, eye-rubbing contributes significantly to disease manifestation.

ALAN N. CARLSON, MD
DURHAM, N.C.

The origins of keratoconus are incompletely understood, but they're likely multifactorial, where keratoconus genetics create a predisposition and eye rubbing contributes to progression. Consider two identical twin brothers with identical genetics. One becomes an alcoholic and the other decides never to touch a single drink, yet still has a genetic predisposition to alcoholism. I believe this explains why only 7 percent of patients who have keratoconus have a family member they know of who also has keratoconus. There may be others in the family with the predisposition but who don't rub their eyes.

We find that as keratoconus progresses, it takes less and less rubbing to impact the cornea and cause further progression. Patients may even get to the point where their disease is so advanced, it progresses without eye rubbing. Eye rubbing may play less of a role in some patients' disease, but it's clearly an impactful behavior in others.

This can be difficult to determine, however. Our ability to ascertain the degree of a patient's eye rubbing through a history is often thwarted when the patients themselves fail to recognize and report their eye rubbing, which has become such an ingrained behavior it's almost unconscious. Patients may underreport eye rubbing for a variety of reasons, perhaps due a lack of recognition or embarrassment. Family members present during the encounter often support a greater recognition of eye rubbing than the patient reports.

When both patients and family members can't confirm eye rubbing, it's often the case that the patient sleeps in a position that applies pressure against the eye with pillow or hand. In some cases, the patient may have been a vigorous eye-rubber as a child. I believe it's possible to set the ball in motion from an early age. I gave a lecture on this topic a few years ago, and an optometrist reported that one of her keratoconus patients had videotaped her infant child in her crib. Sure enough, the baby was digging into her eyes non-stop.

The Signature Rub

For years we thought eye rubbing was related to the fact that keratoconus patients had a higher likelihood of having an allergy and would therefore rub the eyes to alleviate itchiness. However, there are features and motivations of a keratoconus eye rub that are distinct from an allergic eye rub.

The allergic rub usually falls on a lateral, x-y plane with a back-and-forth motion and moderate pressure, followed by the index fingertip rubbing more nasally and then at the caruncle to finish. These individuals tend to rub for only a short amount of the time (usually under 15 seconds) in an "itch-rub-itch" cycle. They report that it's only to relieve itching and they wouldn't rub their eye otherwise.

A keratoconus rub applies vertical pressure on the z-axis. These patients like to put direct pressure on the eyelid and rub in a circular fashion with a pointed instrument, such as a knuckle (the middle knuckle is more common

(Continued on p. 52)

This article has no commercial sponsorship.

Dr. Carlson is a professor of ophthalmology and a cornea specialist at the Duke University Eye Center in Durham. Contact him at alan.carlson@duke.edu.

COUNTERPOINT:
KERATOCONUS IS PRIMARILY A GENETIC DISEASE

GENETICS CAN'T BE OVERLOOKED

There's a strong genetic component to keratoconus, though other factors can be at play.

CHRISTOPHER J. RAPUANO, MD
PHILADELPHIA

The two-pronged hypothesis for keratoconus suggests that an eye-rubbing or a chronic eye trauma component is necessary in addition to a genetic predisposition in order for keratoconus to develop. I'm not convinced of that, however. Though there are definitely patients who rub their eyes and get keratoconus, whether they have a (known) predisposition or not, many patients progress in the absence of (known) eye rubbing. Even after corneal crosslinking, a small percentage of patients will progress. We suspect that some of these patients still rub their eyes or sleep with pressure on their eyes, but it's possible that their keratoconus is so bad that crosslinking isn't enough to stabilize it.

Family History

Genetics plays a key role in keratoconus development, alongside other environmental and mechanical factors. We know the condition occurs with higher frequency in certain ethnicities such as in Asian and Middle-Eastern people,[1] and first-degree relatives of keratoconus patients have a much higher prevalence of keratoconus compared with the general population.[2,3]

Depending on how you define keratoconus, between 10 and 20 percent of these patients will have a family history of the condition. If a family member doesn't have frank keratoconus, there's a higher likelihood that their topography is somewhat abnormal, and this may bring the numbers up to 20 or 30 percent. So, just from family history, we know there's a strong genetic component, though of course cases may be sporadic. I always ask my keratoconus patients about any family history of keratoconus. Frequently, they have a history, but certainly not always.

When patients see me for refractive surgery evaluations, I always ask if they have a family history of corneal problems, keratoconus or corneal transplants, because there have been cases in which patients with perfectly normal-looking eyes get refractive surgery such as LASIK and end up with ectasia. Then it turns out that they have a family history of keratoconus. We think patients with a family history of keratoconus may be predisposed to ectasia after refractive surgery. So, in these cases, we inform the patient about their possible increased risk of postoperative ectasia and may recommend no refractive surgery or may suggest PRK instead.

Seeking Candidate Genes

For decades, we've been trying to find a gene or set of genes for keratoconus. New tools for identifying genetic variations associated with keratoconus such as genome-wide association and linkage studies, as well as gene expression studies and RNA sequencing,[4] have brought us closer to our goals, but the condition's genetics are complex.

Yaron S. Rabinowitz, MD, has been researching keratoconus genetics for years. In 2016, his group reported that single nucleotide polymorphisms associated with the genes *LOX, CAST, DOCK9, IL1RN, SLC4A11, HGF, RAB3-GAP1, TGFBI, ZNF469,*

(Continued on p. 52)

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Dr. Rapuano is a professor of ophthalmology at the Sidney Kimmel Medical College at Thomas Jefferson University and the Chief of the Wills Eye Cornea Service in Philadelphia.

Eye-rubbing

(Continued from p. 50)

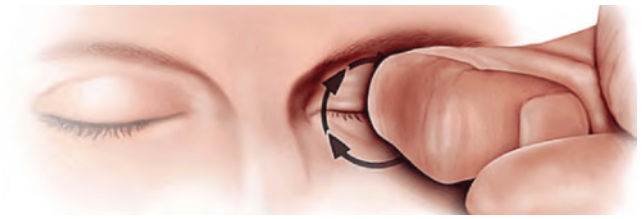

Figure 1. The KC patient will often use a knuckle to generate greater pressure through the center of the lid, applied with circular motion.

than the distal or proximal knuckle) or fingertip. This might last for 10 to 180 seconds, and up to 300 seconds. Sometimes they just like to press on the eyeball through the eyelid.

Keratoconus patients are either unable to explain why they rub their eyes or report that there's just something pleasurable about it. I liken this to scratching a mosquito bite. Scratching a mosquito bite feels very different than scratching an area on the body without a mosquito bite.

When asking patients about their eye-rubbing history, it's important not to ask leading questions. For instance, I'll say, "Show me how you rub your eyes," and they'll go up with both hands and rub their eyes. If they rub one eye, 80 percent of the time, that's the side they sleep on and the eye with the worse keratoconus. Yes, sleeping position, too, can affect keratoconus progression.[1]

This is another behavior that patients often aren't aware of. Certain sleep positions put pressure on the eyes, and over time the cumulative low-to-moderate pressure for several hours each night adds up. Many keratoconus patients even report that they can't sleep unless something's in contact with their closed eye such as their arm flung across their face if they sleep on their back, or a pillow if they sleep on their side or stomach. If their disease is advanced, you'll often find they sleep on their stomach because they can press both eyes into something.

Other Contributors

Keratoconus has also been tied to eyelid laxity and sleep apnea.[2-3] Side-sleeping with the eye pressed to the pillow may cause mechanical and thermal contributions to the eyelid and cornea. I've observed that patients with asymmetric keratoconus are more likely to develop a floppy eyelid on their sleeping side.

I've also seen a number of keratoconus patients with undiagnosed sleep apnea. I studied sleep apnea in keratoconus patients with Preeya K. Gupta, MD, a number of years ago, and we found that keratoconus patients have a higher prevalence of obstructive sleep apnea compared with the general population.[4] There may be some association

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Genetics

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ZEB1, *VSX1*, *COL5A1*, *COL4A3*, *COL4A4*, *FNDC3B*, *FOXO1*, *MPDZ-NF1B*, *WNT10A*, *SOD1*, *IL1B*, *IL1A* and microRNA *MIR184* have been suggested to influence keratoconus, but not all the analyses of these genes completely confirm a role in pathogenesis.[5]

Dr. Rabinowitz's group pointed out that keratoconus likely results from abnormalities in several biochemical pathways. For example, a 2020 genome-wide association study, which he was also involved in, reported that overexpression of the antisense RNA gene *AP006621* may destabilize corneal structures.[6] The researchers noted that this was related to a genome-wide significant locus for keratoconus that they identified in the *PNPLA2* region on chromosome 11. This novel locus reached genome-wide significance in the four-cohort analysis (n=5,853; $p=2.45\text{x}10^{-8}$).[6] (The *PNPLA2* gene, or patatin-like phospholipase domain-containing 2 gene, is a protein-coding gene that encodes the enzyme that catalyzes the first step in triglyceride hydrolysis in adipose tissue.)[7] Interestingly, the group also pointed out that the chromosome 11 locus overlaps with a previously reported but not genome-wide-significant association signal for Fuchs' endothelial corneal dystrophy. Having both FECD and keratoconus together is rare, however. Having said that, we did report 27 cases.[8]

Some other variants that have been identified and linked to keratoconus risk include the rs1042183 variant in the *ALDH3A1* gene in a Polish population, which was found to increase risk;[9] the rs2228557 variant's T allele in the *COL4A4* gene, which was found to act as a protective factor vs. the C allele in an Iranian population;[10] and the rs4898 variant in the *TIMP-1* gene, where the TY genotype or T allele was found to decrease risk of keratoconus in Iranian males vs. the C allele, and was protective for the population.[10]

Associated Conditions

We also suspect that keratoconus patients may have some type of collagen abnormality, since floppy eyelid syndrome and sleep apnea are both seen fairly often among keratoconus patients. The *COL5A1* gene, for example, is related to fibril-forming corneal collagen and to central corneal thickness, which has a strong genetic component. The keratoconus-associated loci *RXRA-COL5A1*, *FOXO1* and *FNDC3B* have also been found to be associated with central corneal thickness.[6]

Atopic disease and Down syndrome are two other conditions associated with keratoconus, but they're also both associated with eye-rubbing, so it's unclear whether it's the disease that's genetically associated or whether these

(Continued on p. 54)

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Eye-rubbing

(Continued from p. 52)

Figure 2. The KC patient may also generate intense central pressure by applying their finger tips(s) to the central lid, often with a circular motion.

between a floppy cornea and floppy soft palate. We also found that patients who have corneal transplants for keratoconus have some inflammatory mediators such as MMP-9 at a higher rate in the cornea, just like people who undergo sleep apnea surgery. There may be more systemic floppiness going on.

We've also reported that patients undergoing keratoplasty for keratoconus have a higher likelihood of being morbidly obese.[5] These patients weighed an average of 31.7 pounds more than age-matched controls (p=0.015). Based on BMI, patients with keratoconus were 1.6 times more likely to be classified as overweight, 2.2 times more likely to be classified as severely overweight and 9.1 times more likely to be classified as morbidly obese vs. controls. However, unlike other patients with sleep apnea, who tend to get a lot better when they lose weight, these keratoconus patients don't usually see an improvement in sleep apnea with weight loss. They're also more likely to have a floppy eyelid.

Deterring Eye Rubbing

Reducing the urge to rub the eyes may help to decelerate keratoconus progression. Patients with Intacs corneal ring segments report discomfort when they rub their eyes, and this serves as a deterrent. I found Intacs more predictable than crosslinking, in terms of improving keratoconus and contact lens wear. Many of my ring-segment patients years ago were able to avoid the need for a corneal transplant, while a few went on to DALK and successful contact lens wear. Counseling patients about the harmful effects of eye rubbing and other activities that cause mechanical trauma to the cornea may help to slow keratoconus progression in some patients.

Large-scale Genetic Testing

Identifying susceptible patients as early as possible would be wonderful. There's a potentially large number of people with the genes for keratoconus—but this isn't the full picture. Take the 23andMe test, for example. This test often tells people they have a risk of developing macular degeneration. There are genes that show you're at risk for AMD, but many people also have genes that prevent or postpone its onset. The test doesn't mention those.

I took the test, and it says I have a risk of developing macular degeneration. I probably got the genes from my 92-year-old father who only now shows early signs of macular degeneration. He probably has the genes for macular degeneration, but he probably also has the genes that postpone or prevent it.

So, for the most part,[6] we don't know what's preventing us all from getting keratoconus, and we're not testing for that. The commercial genetic test kits don't work that way—they only look at genes associated with a particular disease. ◀

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Genetics

(Continued from p. 52)

conditions, like allergies, cause eye rubbing, and the eye rubbing contributes to keratoconus.

Genetic screening to identify susceptible keratoconus patients early on has potential down the line. The AvaGen test from Avellino Labs (for which I'm a consultant) reliably tests for corneal dystrophies, such as lattice, granular and Reis-Bucklers dystrophies, but that's because those dystrophies' genetics are black-and-white: you either have the gene and therefore the dystrophy, or you don't. AvaGen assigns a low-medium-high keratoconus risk score based on numerous mutations, but in the fairly small number of tests I've done recently, it's unclear to me how helpful it was. As with any genetic test, as they get more subjects and more diverse populations, I'm sure the results will become more meaningful.

Further well-powered genetic research in large and diverse populations will help us learn more about keratoconus etiologies and guide new treatments. ◀

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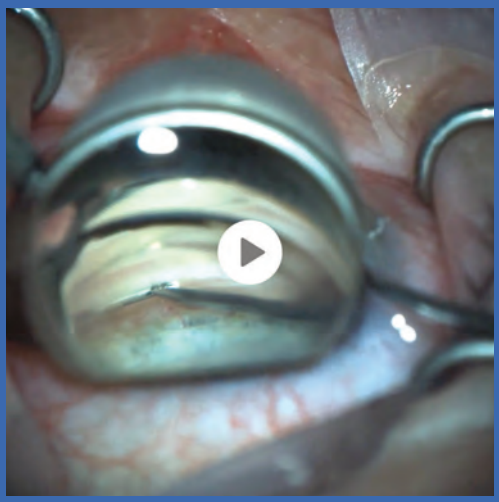

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HOW TO CAPITALIZE ON THE LASIK BOOM

LASIK continues to gain in popularity, and some refractive surgeons are booked for months or even years to come.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

In recent years, laser vision correction procedures, specifically LASIK, have increased in popularity. In fact, the Refractive Surgery Council has reported that the laser vision correction procedure volume for the fourth quarter of 2021 was 190,509, which is a year-to-date increase of 32 percent over 2020. The total procedure volume for 2021 topped 833,000 for the first time since the council began tracking laser vision correction procedures in 2015.[1]

Why are LASIK Rates On the Rise?

According to John Vukich, MD, who is in practice in Wauwatosa, Wisconsin, there are several reasons that LASIK rates increased starting in 2020, and the effects of the pandemic are at the top of the list. "During the pandemic, people were working from home. They were wearing masks, and if they had glasses, there was the potential for masks fogging the lenses," he notes. "And, then, there were government incentives that provided some discretionary income, and people weren't dining out or traveling. All of that did, in fact, increase LASIK volumes. This was seen across the board by all providers of LASIK. Now, the question that we have is whether there will be some return to pre-pandemic numbers. The economic incentives have dried up, and the majority of people aren't wearing masks anymore. Was this just a temporary blip fueled by circumstance, or was this the renaissance of refractive surgery? The answer is unclear."

Edward E. Manche, MD, director of refractive surgery at Stanford University, agrees, and adds that it was easier for patients to attend medical appointments when working from home during the pandemic. "I also think that people became more conscious of their facial appearance when they were on Zoom daily," he says. "Instead of putting in contacts every day, they elected to spend money on laser vision correction. I think all of the above are potential reasons why the volume increased."

How to Capitalize on the Boom

Now that most people are back to work in the office and don't have as much disposable income because travel and other activities have resumed, how can ophthalmologists keep the boom going? Some practices are choosing to advertise, while others are relying on word of mouth. "My practice doesn't advertise at all," says Dr. Manche. "We have a web presence, but 90+ percent of our patients are word-of-mouth referrals. We also get some physician referrals, as well."

Dr. Manche adds that the decision of whether to advertise depends on the practice's style. "There are very busy practices who do a lot of advertising," he avers. "It's just not the style of my practice. I'm in a unique setting here, so we don't do it. However, some doctors have increased their advertising because the volume has ticked up, and they want to capitalize on it while the interest is there."

Dr. Vukich believes that the best advertising for LASIK is word

This article has no commercial sponsorship.

Dr. Manche is a consultant and performs sponsored research for Johnson & Johnson Surgical Vision. Additionally, he performs sponsored research for Carl Zeiss Meditec. **Drs. Wilson** and **Vukich** have no relevant financial interests to disclose.

of mouth, but that other forms of advertising may be needed. "Peer groups share their experience with their friends and their acquaintances," he notes. "The results have always been excellent and have actually never been better. With the latest generations of instrumentation, we can achieve a very predictable outcome and high level of quality. So, now, there's been a resurgence of interest, and patients who've had it will continue to spread the word. So, what can we as surgeons do proactively? What are the things that are within our control? I think that there is now a reason to believe that we can once again start to advertise to consumers. We need to advertise that we have this capability. Many practices cut back on their LASIK advertising simply because, when the market was down, there was less income to devote to that. It was really kind of a downward spiral for a while. As a group, we need to acknowledge that this is an important service and a high-quality product."

He also notes that the decision is associated with an increased quality of life. "I think there's a trend toward the 'experience economy' that we're seeing with the prime demographic that's looking at LASIK," says Dr. Vukich. "These are individuals who may have delayed buying a home. They may have student loan debt. However, they will make it a priority to go on vacation or plan another memorable quality-of-life experience. LASIK is clearly an every-waking-moment of every day quality-of-life experience. That's the reality that we need to continue to make sure people understand."

Steven E. Wilson, MD, from the Cleveland Clinic, says that his practice did a lot of marketing in the early days of LASIK. "We got one of the first microkeratomes, which was the ACS," he recalls. "When the Hansatome came out, we converted to that. During this time, we did a lot of marketing, which consisted of radio ads and e-mailing patients of the Cleveland Clinic. We also marketed to employees, who received a 20-percent discount at that time. After about 10 years, we basically stopped marketing because people began coming just from word of mouth. Patients would visit the Cleveland Clinic and see that we had a refractive surgery practice. It just kind of fed itself."

> **"So, now, there's been a resurgence of interest, and patients who've had it will continue to spread the word. So, what can we as surgeons do proactively? … I think that there is now a reason to believe that we can once again start to advertise to consumers."**
>
> ***— John Vukich, MD***

Dr. Wilson adds that his practice has had some ups and downs in volume, with the worst period being during the crash in 2008. "Then, the volume slowly came back and was pretty consistent for several years," he says.

In 2022, the Cleveland Clinic has seen a huge increase in LASIK cases. On January 1, they announced that all employees who were on Cleveland Clinic health insurance could undergo bilateral LASIK or bilateral PRK for $150 out of pocket. The rest of the fee is covered by Cleveland Clinic insurance. "Since that announcement, every one of my surgery days has been completely filled," Dr. Wilson says. "I'm booked out for actual surgery for over six months, and I'm totally booked for the next year just for screenings. We have a list of people who want screenings when more spots open up next year. That's not just me; that's all of our refractive surgeons. So we're doing the most procedures we've ever done."

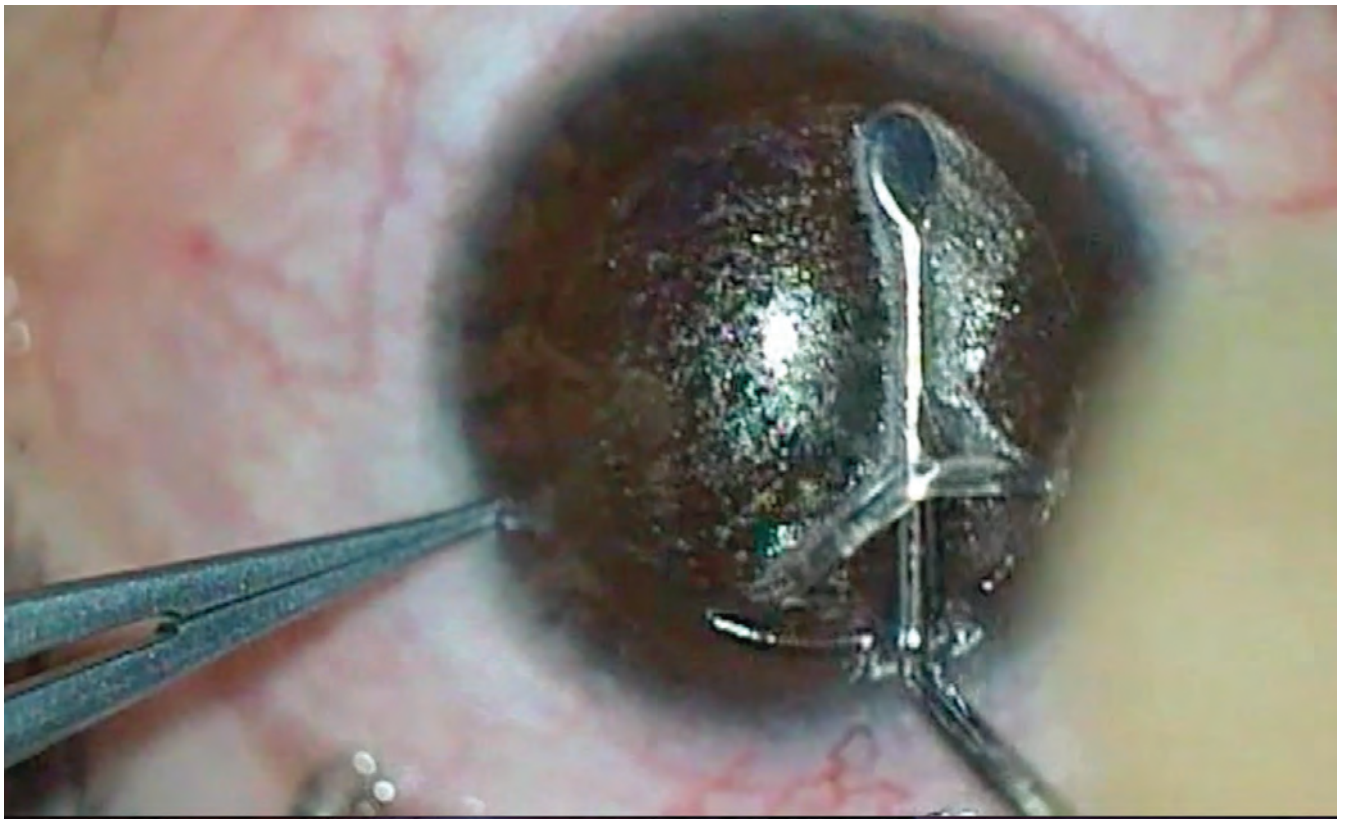
LASIK: The Procedure of Choice

LASIK was approved by the FDA for use in 1995 and has remained at the forefront of refractive surgery since that time. According to Dr. Manche, the majority of patients still prefer LASIK, even though new procedures are available. "In my practice, refractive surgery volume is about 80 percent LASIK, 15 percent PRK, and about 5 percent SMILE," he says. "LASIK is still the dominant refractive surgical procedure, both in my practice and nationwide."

He believes that this is a testament to how effective the procedure is. "I've been performing PRK and LASIK for 27 years," he says. "It has worked incredibly well, even from the early days. Obviously, it's significantly better now. It's safer and much more sophisticated. A lot of innovations have occurred along the way, so it's not the same LASIK surgery we did back in 1995. Patient satisfaction is 95+ percent. It's really hard to displace something that has such a high success rate."

Dr. Wilson agrees, noting that no other procedure is as precise, safe, and comfortable for the patient as LASIK. "Additionally, there's instant gratification, typically by the next morning," he notes. "I still do quite a bit of PRK, but I perform these procedures in patients who aren't good LASIK candidates, either because their cornea is too thin for their level of correction or because they have inferior steepening on their corneal topography—not keratoconus, just inferior steepening. With PRK, patients' vision won't reach the final outcome for at least five days to two weeks. After about five days, most PRK patients are able to drive, but it sometimes takes even longer. In comparison, most LASIK patients are driving the next day."

Dr. Wilson's practice owns a



Though LASIK remains the most popular refractive procedure in the United States, small-incision lenticule extraction is in its beginning stages, and some experts think it has the potential to be improved and eventually challenge for the crown.

laser for SMILE. "That laser is my favorite flap-making laser, and two of my colleagues perform some of these SMILE procedures, but it's never going to reach the volume of LASIK because it's more complex, more things can go wrong, and some patients have delayed visual recovery," he opines. "Additionally, if you want to enhance patients after SMILE, there are issues with that. Companies are working on technology to try to repeat SMILE, but that's problematic, and you can end up with a fragment of the lenticule left inside the cornea. The simple answer is that there's nothing that provides the same immediate gratification that LASIK does with a similar safety profile."

According to Dr. Manche, LASIK is the gold standard, but SMILE is a strong contender. "SMILE is definitely making a run," he says. "Of all the things that could replace LASIK, SMILE might in the future. SMILE is currently in its infancy, and only one company's laser is currently approved for use in the United States. Other companies are throwing their hats in the ring and are starting to test their own systems, which is how I believe you spur advances. It happens when multiple companies are developing the technology. So, hopefully it gets better and better. If I could look into my crystal ball, I'd say that LASIK is still going to be done in the majority of cases down the road. It may get to a point where there are equal numbers of SMILE surgeries done as LASIK in the United States, but I think it's going to take a while for the results to get as good as we see with LASIK."

Dr. Vukich adds that the outcome with LASIK is indisputably excellent and consistent. "In the past, there were some vocal opponents of LASIK who were trying to say it was a dangerous procedure that didn't have the outcomes that we thought were safe," he recalls. "But, the test of time has proven them wrong. This is a safe procedure that is very predictable in terms of its outcome. The technology that we have now provides an even more consistent and excellent outcome. It's always been good, but, like with anything technology-driven, it's now faster, better and more predictable. That's just the nature of the technology that drives this type of correction. It's getting incrementally better from a very high level already. Incremental improvements are obviously what we would expect along the way. So why has it stood the test of time? Because it works, it works well, and it provides a very satisfying outcome."

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THE NUTS AND BOLTS OF PREMIUM IOL PRACTICE

Experts discuss what sets some practices apart from others in the world of premium lenses.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

If you decide to venture into the world of premium surgery or are looking for ways to improve how you're already offering these services, cataract surgeons say it's important to be committed in order to do it right. Incorporating premium services requires a degree of business know-how and some logistical changes, including technology investment, scheduling and clinic flow alterations, and providing additional education for both patients and staff.

"You need to believe you're actually giving the patient something that can benefit them and improve their life, because if you don't believe in the technology yourself, it's hard to present these options to qualified patients," says Kendall Donaldson, MD, of Bascom Palmer Eye Institute in Miami.

In this article, cataract surgeons discuss their approaches to premium services and how to shape a practice that supports patient happiness at every step.

Avoid the Sales Pitch

"The original challenge was finding the perfect candidate for some of the first- or second-generation presbyopia-correcting lenses. Now, the challenge is tailoring the discussion to the patient so they can decide which of the appropriate lens implants is best for them," says Sumitra Khandelwal, MD, of Baylor College of Medicine in Houston. "It's important to let the patient know all of their options."

When having this discussion, experts say to avoid sounding as if you're giving a sales pitch. "Sales-pitch-style discussions offend many patients," says Dr. Donaldson. "Be honest about what the technology can offer the patient and discuss the limitations as well as the benefits."

Kevin M. Miller, MD, of the Stein Eye Institute at the University of California Los Angeles, says there's an overemphasis on the IOL in the world of premium surgery. "The word 'premium' implies that a standard lens is somehow subpar, which of course, it's not," he says. "We call premium IOLs 'specialty' lenses in our practice because they fit specialty needs. They're not for everybody.

"The emphasis should be on doing what's in the best interests of the patient," he continues. "Each patient who comes through our office door can be approached as a premium patient because we can achieve premium results by managing astigmatism even if we'll be implanting a monofocal lens. In the end, what determines how well a person sees is the health of the eye and their refractive state.

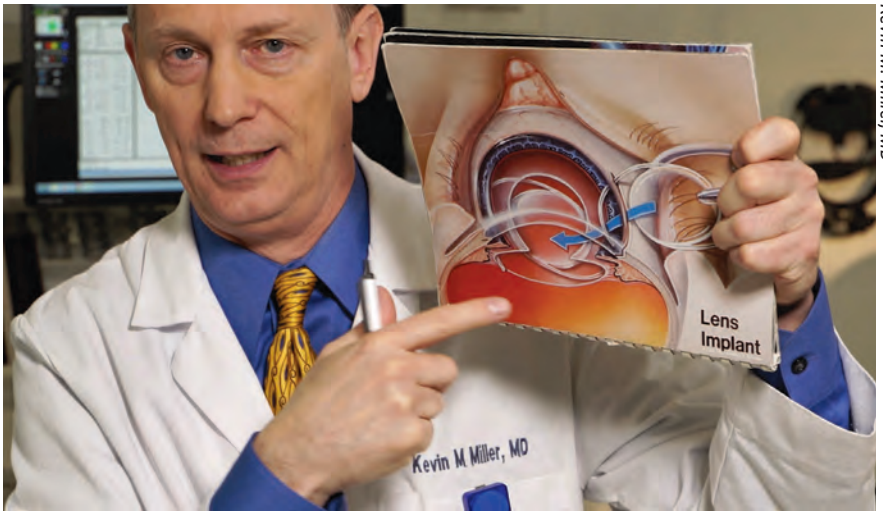
"Much of your discussion should revolve around pathologies in the eye, the patient's lifestyle, and their wants and their needs," Dr. Miller points out. "There are some patients who are quite content wearing reading glasses and trying to upsell them on a multifocal lens may be the wrong thing for them."

Many practices separate the lens

This article has no commercial sponsorship.

Dr. Donaldson consults for Alcon, Johnson & Johnson Vision, Carl Zeiss Meditec, LensAR and Bausch + Lomb. **Dr. Miller** consults for Alcon, Johnson & Johnson Vision and Oculus USA. **Dr. Khandelwal** consults for Alcon, Bausch + Lomb and Zeiss. **Dr. Thompson** discloses financial relationships with Alcon, Bausch + Lomb, Rayner, Zeiss, Vance Thompson Vision and Absolute Presbyopia.

and money discussions. After Dr. Khandelwal gives her lens recommendations to the patient, the patient speaks with the practice's surgical coordinator to review the costs for the lenses the patient is a candidate for. "Then, during the preop visit, we sit down and confirm the lens implant, and I answer any questions," Dr. Khandelwal says. "I always tell my patients, 'It's your decision, and it's okay if you pick a standard lens covered by insurance. You'll still see better than you do now.' That way they don't feel pressured into anything by their surgeon."



Kevin M. Miller, MD

All potential cataract surgery patients at Kevin M. Miller, MD's practice at the Stein Eye Institute at the University of California, Los Angeles, watch a 40-minute educational video to learn about the eye, cataracts, cataract surgery, lens options, complications and what to expect. Educational videos for patients are one way to standardize what's said to the patient, and the video can be documented in the patient's chart.

Additional Chair Time

Premium lens candidates generally require more chair time than patients receiving standard lenses, such as a patient whose retinal pathology limits their choice of implant. Experts say it's important that your schedule allow for that additional time, or that you have a dedicated staff member such as a surgical coordinator who can spend time with patients, so they can make the best choices for themselves. "Sometimes this requires logistical changes in the way we schedule patients," Dr. Donaldson notes.

You may be able to streamline some of this process with supplemental material and by educating patients before they come into the office. "Our website has patient information on cataract surgery and lens options, and even just identifying a patient as a cataract consultation allows us to send them information electronically," Dr. Donaldson says. "Having these educational materials available for the patient before they come see us increases our efficiency."

Dr. Khandelwal points out that if you don't have educational material ahead of time for the patient, give it to your patient the day they're evaluated in the clinic and let them go home to read it and then follow up with somebody, such as the surgeon, optometrist or surgical coordinator.

Keeping your recommended options simple is often most helpful for the patient, experts say. "We weed out patients who wouldn't be appropriate for certain lenses and limit their options because we know they might have more glare or halos—though we can't really determine how much they'll notice those," Dr. Donaldson says.

"I give my patients a handout that has everything I discussed with them," Dr. Khandelwal says. "It includes pricing, so they have a chance to actually look at it before they talk with my surgical coordinator. Having things on paper is so important because patients get really confused, and they're given so much information during a cataract evaluation—important dates, risk factors, lens implant information, etc."

Dr. Khandelwal also says it's good to have at least two different times when patients can ask questions. "This is important for practices," she says. "If you see a patient for the first time, and they've never heard of the different lens options, and that's the only time they're going to ask their questions, it's very hard for them to understand what they're getting into. It's key that they hear this information twice and get to ask questions at least twice. That could be with you, the optometrist or the surgical coordinator."

Educational videos are another way to inform the patient, save the surgeon time and provide consistency. Dr. Donaldson and Dr. Miller both created educational videos in which they discuss cataract surgery and lens options.

"I created a nine-minute video that reviews all of the lens options for patients, so I don't have to repeat that to every patient throughout the day," Dr. Donaldson says. "It's been a great time investment. When they're in the exam room waiting for me, they're given an iPad to watch the video. (It's also available on our website.) They can watch it while they're waiting for me and while they're dilating, and it goes through all their choices. It's very helpful and has made my practice more efficient."

She says you can also document in the patient's chart that they saw

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.

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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.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
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Initial U.S. Approval: 2011

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

EYL.20.09.0052

the video. "You know exactly what's been told to the patient, as far as benefits, limitations and technology, and that the patient's specific lens options will be reviewed with the physician. Then, I can walk in and say, 'Oh, now you're a bit familiar with it, and we can go over in more detail what would be most appropriate for you.' They usually have some questions lined up after the video."

Patients coming for their preoperative evaluation view Dr. Miller's video during their encounter. He says that during the 40-minute video, he discusses the nature of cataracts, cataract surgery, astigmatism management, femtosecond laser use, intraoperative refractive guidance systems, postoperative refractive enhancement, risks and complications.

"They get the whole spiel, including a section for those interested in taking part in our patient-based research at the University of California's Stein Eye Institute," he says. "It's a bit like taking a sip of water from a fire hydrant, but this way the concepts aren't completely foreign when they meet with me subsequently. On the initial consultation, the one before the preoperative visit, they also receive a one-page handout that describes all our refractive services and the associated costs. We get sticker shock out of the way early. If they don't come back, we haven't wasted any time."

Consistent Messaging

"Patients may not remember 90 percent of what I say or what anybody in my office says, but they'll pick up on any discrepancies in a heartbeat," says Dr. Miller. "You really have to make sure your messaging is consistent. Everything in our office is well-scripted. We have documents and forms to give to patients, and we're very clear about what our services are over the phone."

Vance Thompson, MD

The Atrium at Vance Thompson Vision in Sioux Falls, South Dakota. Customer service is important in any practice, but it's especially key when patients are paying so much out of pocket. When patients enter the clinic, they're greeted by the First Impressions team. After the front desk collects patient information, the team enters a description of what the patient is wearing and where they're sitting so the technician can walk right up to the patient and greet them. Dr. Thompson's practice uses a seating chart for their Atrium similar to that of a restaurant for reference.

Dr. Donaldson agrees. "Patients ask a lot of questions along the way, and you want to make sure they're receiving a consistent message from the time they walk into your office, through the exam and imaging, and sitting with the surgical coordinator," she says. "You want one consistent message, so the patient doesn't feel overwhelmed.

"When I finish my cataract consultation, I write a specific recommendation in my plan so that when my staff see the patient, and when we're taking measurements, they can propagate the same message about what I've recommended instead of talking about all the other lenses again," she says. "To ensure that consistency, your staff need to be well-educated too, and also buy into the technology."

Dr. Khandelwal says her practice hosts lunch-and-learns for the staff whenever a new technology comes out. "Our technicians are really excited about new lens implants," she says. "They really notice how happy the patients are after these procedures."

Dr. Miller's practice has monthly staff meetings. He says they frequently perform walk-throughs from the patient's point of view.

"We roleplay how it looks from the patient's perspective at each touchpoint, starting at the front desk," he explains. "A patient might say, 'Hey, I hear you guys use these lasers? What's that all about?' And the front office staff will tell me what they would say to the patient. I might say, 'Okay, refine that answer a bit.' We do this through the entire process, and we do it continuously because we're constantly bringing new people on as some staff move on to other jobs."

Dr. Miller also has his staff go to the operating room so they can see what goes on there. "Patients often ask the front office staff what surgery is like," he says. "They can't answer those questions if they've never been there themselves, so we bring them down to see everything live. I also have every staff member watch the educational video I show to patients, and at the monthly meetings we talk about patients who were a problem in the past month and go over talking points for the staff. It's just a matter of continuous education."

Investing in your team will pay off, doctors say. "When you look at the clinic flow, so much of the patient's time is spent with your team," says Vance Thompson, MD, of Vance Thompson Vision in Sioux Falls, South Dakota. "The majority of the functions in a clinic are delivered by staff. We have training classes, retreats, manuals and forms, and then we have employee-to-employee training for new employees working in the same job."

Simple Pricing Structures

Physicians agree that a simple pricing structure usually works best for a practice and its patients, but every practice is unique. "Having a global fee has worked the best for us," says Dr. Thompson. "We used to not include the enhancement and the patient would simply pay extra, but that didn't go over well."

Two commonly used models are an à la carte system or a package. "With à la carte pricing, the practice usually charges the patient for the surgeon fee and a lens," Dr. Khandelwal explains. "There are several things to factor into this model though. For one thing, premium lenses cost more money than standard lenses, so the cost of the lens must be included in your pricing. Your time is also valuable—these patients expect a certain outcome and you may have to see them more often. Some of these premium lenses may make small things, such as ocular surface disease or posterior capsule opacity, more apparent, so it's important to calculate how much time you're spending on that."

Dr. Khandelwal's practice finds package pricing easier. In this model, enhancements such as refractive cataract surgery, LRIs or lens exchanges are included in the package (e.g., standard cataract surgery, astigmatism correction or presbyopia correction packages). "Pricing really depends on each practice and on the market rates," she notes. "You can ask your colleagues about market rates, but not everyone will feel comfortable doing this."

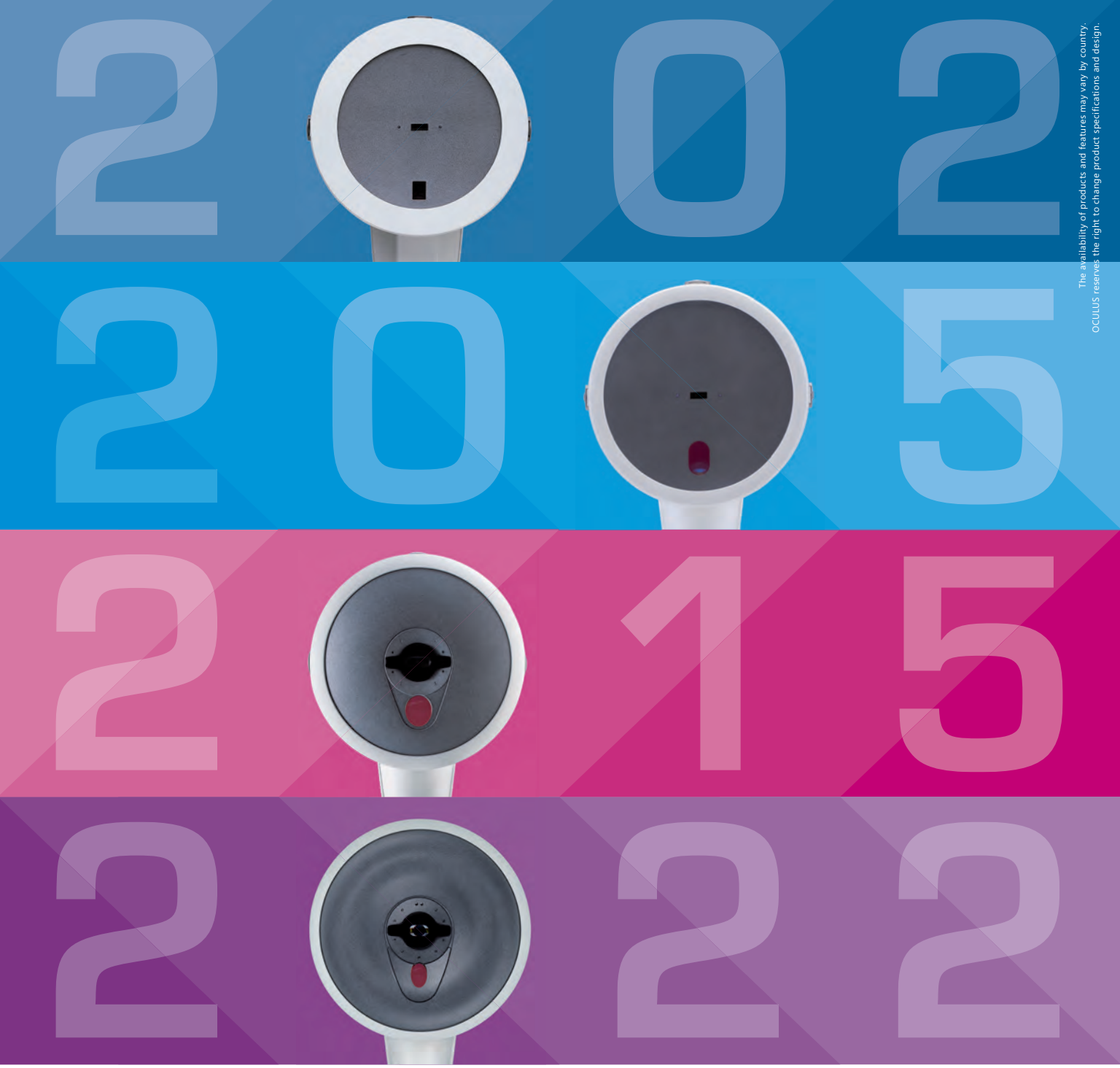
Dr. Khandelwal performs any enhancements herself. "I'm a cornea specialist and a LASIK surgeon, so doing LASIK or PRK is easy for me since it's already incorporated into my practice," she says. "We own our excimer laser and are prepared to do enhancements on our patients.

"If you're not a corneal refractive surgeon, you have a couple of options," she continues. "You can learn how to do basic PRK, or you can talk to a neighboring practice that owns its own laser and work out a model where they can assist you with enhancements for your patients. We often do that for our referring doctors who implant lenses but don't have access to a refractive laser for corneal enhancements. In those cases, we discuss with them the best option for the patient's best outcome."

"At Bascom Palmer, we have a pretty simple pricing structure, which is key because patients can become overwhelmed," Dr. Donaldson says. "We have our standard lens options that are covered by insurance and those outside insurance. We have two levels of upgrades. The first is astigmatism correction, where we would use distance lenses, near lenses or monovision. The second is presbyopia correction. PanOptix, Synergy, Symfony, Vivity or any of the various presbyopia-correction options are all the same price. It's pretty simple. Any enhancements are included in the price of the upgrade for one year, so we aren't charging for LASIK or PRK. Refractive enhancements are included and one year covers most people."

"If appropriate patients want an EDOF or multifocal lens, they pay the hospital for the lens," says Dr. Miller. "I don't make any money from the sale of a specialty lens, so there's nothing pushing me to sell lenses. It takes a lot of the financial bias away. I don't have to figure out, for example, if I can 'get away with' implanting a multifocal lens into an eye with a mild epiretinal membrane. I simply don't do it because it's not in the patient's best interest."

His practice charges patients based on services provided and the hospital charges for devices. There are four services. The first two are related to astigmatism management: one option with a diamond knife or metal blade and the other with a femtosecond laser. The third option involves the use of intraoperative refractive guidance technologies such as Callisto, Verion and ORA. "We have all three and talk to patients about which device or devices we'd like to use or that would be optimal for their particular situation. They can sign up to have a guidance device used if they want. Otherwise, we just do



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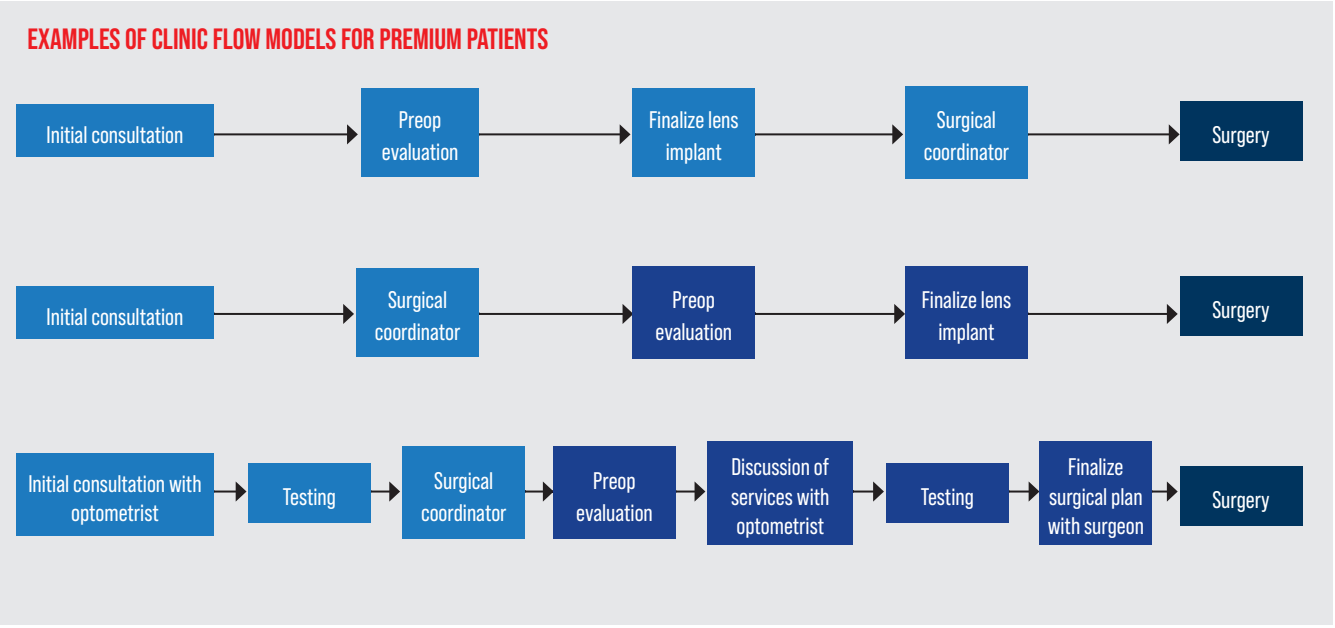

Some practices conduct the initial consultation and preoperative evaluation as separate visits (middle, bottom), and others do it all in one day (top). (Boxes of the same color are within the same visit.)

it the old-fashioned way. For refractive guidance, patients pay a certain amount of money to the physician, a certain amount to the hospital, and a certain amount to the lab for the extra work performed."

The fourth service is postoperative refractive enhancement. "If patients sign up ahead of time for postoperative refractive enhancement, they get a laser refractive enhancement for 20 percent of the price they would pay if they came to us otherwise," he says. "Most of the time, we're not going to need to do an enhancement because the refractive results will be good. However, if there is a small refractive error in the end and the patient needs glasses for best visual acuity, signing up ahead of time for the postoperative refractive enhancement service would then have been a good idea. We'll do a touch-up PRK or LASIK once they're stable."

Plan for Unhappiness

"You have to have a plan for dealing with occasional unhappy patients," Dr. Miller says. "They've spent a lot of money and time, and they're unsatisfied. The first time you get an unhappy patient, it's upsetting, and you may think that doing refractive cataract surgery is too much work. Good communication is key. Speak honestly with the patient, find out what's keeping their vision from being satisfactory, and talk objectively about costs. You need to be able to manage the occasional patients who don't have optimal results and work with them. I can take almost anybody who's not happy and make them happy eventually."

"This is why we make the phone calls," says Dr. Thompson. "We want to ensure that patients remember what we told them preoperatively—that there can be blurry vision, that fine-tuning is often needed postop and that there's a neural adaptation time period. We cover this in detail preop but also deliver this postop to make sure the patient is happy."

Clinic Flow Models

There are many different clinic flow models, and they vary by practice. "Some people do the cataract evaluation and then bring the patient back for the preop while others do it all in one day," Dr. Khandelwal explains. "In some models, the optometrist does the preop or the counseling and then surgeon meets the patient."

"We target the cataract surgical evaluations in advance of the clinic," says Dr. Donaldson. "When the patient is seated in the exam room waiting for the physician, they're given an iPad with a nine-minute video explaining cataract surgery and the potential lens options. Following the cataract surgery consultation, they're given a package of information to review and they receive a follow-up phone call within one week to review any questions and discuss whether they're ready to proceed with surgery. They're also given the surgical coordinator's information at the time of their visit so that they may move forward on their own schedule, if they prefer. We're very cautious to not 'oversell' and let the patient lead the process with their desires and expectations for their cataract surgery."

Dr. Khandelwal's practice has two models, depending on where the patient comes from. "Most patients

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are referred to me for cataract evaluation, and I start the discussion of lens implants that day for those without any prior knowledge," she says. "I give them a handout and have them talk to my surgical coordinator. Then, they come back another day for the preop visit where we finalize the lens implant decision.

"The second model works well with our trusted referral sources, both optometrists and ophthalmologists, who really know the different lens implants out there and counsel patients," she continues. "The patients come to me on the day of their evaluation, but because their referring doctor has spoken with them, and they already have an idea of which lens implant they want, it's also their preop day. We often go with what the referring doctor said, but sometimes I change the plan. At the end of the day, the referring doctor is looking to me as a surgeon who will implant the best lens for their patient."

Patients see an optometrist for their initial consultation at Dr. Miller's practice. "Patients also get some labs done and, if they're a candidate for cataract surgery, they see a surgical coordinator to schedule surgery," he explains. "If we can fix their vision sufficiently with glasses or contact lenses, we'll do that instead of performing surgery.

"The preoperative evaluation occurs two weeks before the surgery," he continues. "The patient sees an optometrist, and then goes to a video room to watch an educational video. The optometrist then gives them a preliminary walkthrough of all the services offered and the patient selects or deselects services. Then, they go off for more testing relevant to the cataract operation, such as lens power calculations, corneal tomography, and a macular OCT if they're considering a multifocal lens. They'll sometimes come back to have the optometrist clarify things. I then answer any remaining questions when I see them and we finalize the surgical plan, which might also include a conversation about MIGS devices, capsular tension rings or a dozen other things. When I'm finished, we all sign the surgical and financial consent forms, and the next event is the surgery."

Vance Thompson, MD

Vance Thompson, MD, of Sioux Falls, South Dakota, is teaming up with Kathryn Hatch, MD, of the Massachusetts Eye and Ear Infirmary to host a course called Absolute Presbyopia on January 12-13, 2023, in Napa Valley, California. The course's goal is to teach physicians and their staff about the steps of the premium IOL journey.

Dr. Thompson's private practice has a First Impressions team that collects and documents patient information during an initial phone call—including the patient's favorite beverage and music. "We have Pandora in each of our exam rooms so we can have the patient's favorite music playing when they enter the room," Dr. Thompson says. Patients receive an information packet in the mail after booking their appointment. Dr. Thompson's office also verifies the patient is in their network.

The First Impressions team greets the patient when they come in (and aren't on the phone with other patients). "We have fresh cookies, coffee and water available for our guests," Dr. Thompson says. "After collecting more information, the team enters a description of what the patient is wearing and where they're sitting so the technician can walk right up to the patient and greet them. We have a seating chart of our Atrium similar to a restaurant that we reference."

Patients undergo testing (including Epic, Lenstar, OCT, Pentacam and Tearlab osmolarity) before their exam and consultation with the doctor, where Dr. Thompson "matches the implant technology with their hopes and eyes." The patient sees the surgical coordinator to schedule surgery, discuss postop drop options and fill out financial forms and consents. Then, they go over financial information.

"We use our Financial Information and Consent to Upgrade to Refractive Diagnostics for Refractive Cataract Surgery forms," Dr. Thompson explains. "This clearly explains the difference between the standard charges and the refractive charges. The patient will walk out, personally escorted by the surgical coordinator, with a very good idea of what the surgery will cost them.

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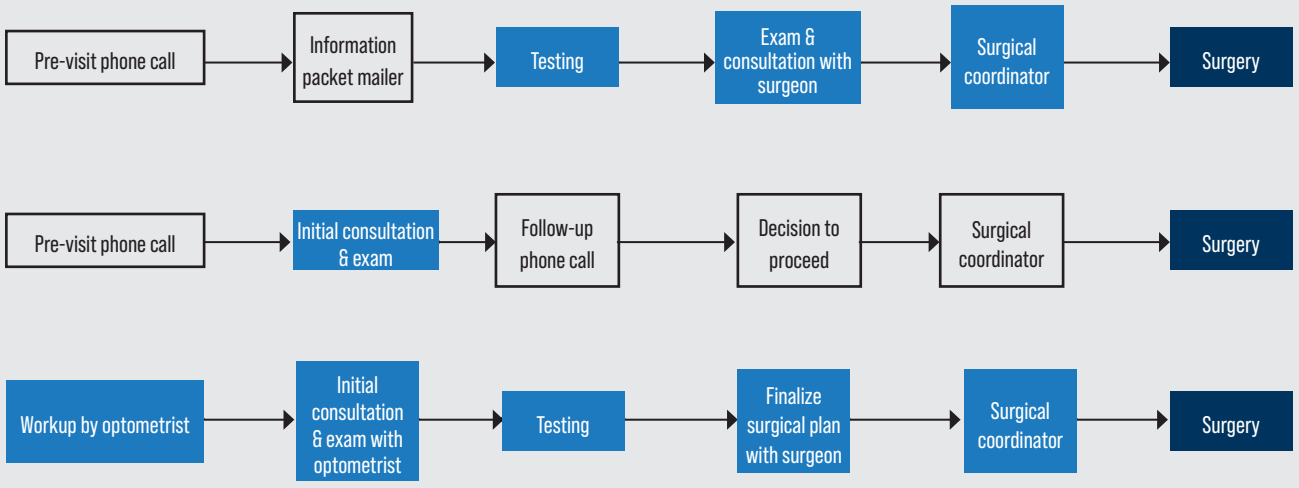
EXAMPLES OF CLINIC FLOW MODELS FOR PREMIUM PATIENTS



We also have financing options to help with the cost. Once their surgery is scheduled, the counseling team sends the patients a text with a link to a video that informs them what to expect in the time leading up to their surgery."

The team calls the patient later on to set up a postop appointment with Dr. Thompson's practice or a local provider. They send additional videos about what to expect on the day of surgery and after (e.g., that it's normal to have some blurry vision or for the eyes to feel scratchy), as well as a one-week postop video in addition to their exams, a surgery center experience survey and "touch-base" phone calls if they're not being seen at Dr. Thompson's practice.

Pearls for Newcomers

"Adding premium lenses to your practice is one of the most rewarding things you can do," Dr. Thompson says. "There's a high rate of satisfaction with premium IOLs—not just for patients, but for the surgeon, staff and community. Patients love that you're presenting them with all their options and delivering what they want. Staff love the professional growth since they become specialists in their area of emphasis."

Here are some pearls for incorporating premium lenses into your practice or improving your existing services:

• ***Start with toric lenses.*** "Someone who's trying to get into premium lens surgery usually starts with toric lenses because they're much more forgiving, as far as any side effects such as glare or halos," Dr. Donaldson says. "You don't have to manage any of the potential dysphotopsias we see with multifocal lenses."

"There are basic things you need to learn if you're going to perform refractive cataract surgery—making a reference mark on the limbus to compensate for recumbent torsion, marking the steep axis, aligning a toric lens in the eye, and ensuring that the lens stays aligned when you remove the viscoelastic," says Dr. Miller, "but patients with astigmatism are generally easy to please. Even before you start with toric lenses, hone your astigmatism management skills by placing phacoemulsification incisions on the steep axis and performing peripheral corneal relaxing incisions."

• ***Invest in the preoperative technology.*** You'll also need to invest in preoperative technology, such as topography and tomography. "The IOLMaster 700 has been key for us because it has advanced formulas built in, including the Barrett formula," says Dr. Donaldson. "We use it in addition to topography and tomography images, and we like them all to match."

• ***Learn the business.*** The business side of premium lenses can be complicated. Experts say you should take the time to learn everything that's involved. Dr. Thompson notes, "I'm offering a course with Kathryn Hatch, MD, called Absolute Presbyopia, where we teach doctors and their employee implementor every step in the premium lens journey." The first course takes place January 12-13, 2023, in the Napa Valley.

• ***Choose easy first patients.*** "I always say to start with a lens you believe in, with the smallest side-effect profile and with a patient who has reasonable expectations," says Dr. Khandelwal. "A patient who has a pristine cornea and a pristine retina is a good candidate. Once you do your first premium lens, you'll gain a lot of confidence if it's a great outcome. If you pick a difficult case the first time around, you may feel as if you don't want to do these lenses anymore, but these are really good lenses and have

(Continued on p. 90)

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Diagnosing Abusive Head Trauma

Identifying ocular manifestations of physical abuse could save a child's life.

ZACHARY A. KORETZ, MD, MPH, DELU SONG, MD, PHD
ERIC D. NUDLEMAN, MD, PHD
SAN DIEGO

Abusive head trauma is a subset of non-accidental trauma that's responsible for significant morbidity and mortality in infants and children. Ophthalmologists may be asked to examine children for signs of AHT, therefore it's important to recognize ocular findings suggestive of physical abuse. Here, we'll describe the signs and symptoms of AHT to look for when these children present.

Pathogenesis of Ocular Injuries in AHT

The incidence of AHT in infants less than 1 year old is approximately 30 per 100,000.[1] Nearly 70 percent of survivors of AHT have long-term neurologic sequelae.[2] The injuries are thought to be caused by rapid acceleration and deceleration caused by forceful shaking or direct head impact or both, with shearing forces at the vitreoretinal interface resulting in the typical intraocular manifestations.[3] This damage is likely to occur in areas of strong attachment such as retinal vessels, vitreous base and the macula. The most common ocular manifestations of AHT are multi-layered intraocular hemorrhages extending to the retinal periphery, perimacular retinal folds and fibrosis, and traumatic retinoschisis.[3-5] Typical extraocular injuries include diffuse unilateral or bilateral subdural hemorrhage, and diffuse brain injury, especially in the absence of significant external injuries.

> **In some patients where the pupil exam is needed for neurologic monitoring, it may be possible to dilate one eye at a time using a short-acting mydriatic agent to preserve the ability to monitor pupillary reactivity.**

Other contributing factors include hypoxia, anemia, reperfusion, autonomic vascular dysregulation, significant shifts in sodium balance, coagulopathy and elevated intracranial pressure.

Examination

Clinical findings in victims of abuse are variable, ranging from nonspecific ailments to acute life-threatening complications, such as severe respiratory distress, intracranial hypertension, loss of consciousness, seizure and shock. The classic triad of AHT is subdural hematoma, cerebral edema and retinal hemorrhage. Ophthalmologists should be aware of "red flags" that may indicate abuse, including poor nutrition, irritability, altered mental status, respiratory impairment, multiple fractures (especially in different stages of healing) and varying degrees of bruising.

A dilated fundus examination with indirect ophthalmoscopy should be performed to evaluate for intraocular signs of AHT. Additionally, a slit-lamp examination is helpful to identify signs of anterior segment trauma such as hyphema. This examination should preferably occur within 24 to 48 hours of initial presentation as intraretinal hemorrhages may resolve rapidly within days after the injury.[6] However, it's not possible to precisely determine the timing of injuries based on examination. In some patients where the pupil exam is needed for neurologic monitoring, it may be possible to dilate one eye at a time using a short-acting mydriatic agent to preserve the ability to monitor pupillary reactivity. If pharmacologic dilation is entirely contraindicated, it's still advisable to attempt an undilated fundus examination rather than forgoing examination until pupillary dilation is permissible. Prior to pharmacologic dilation, perform an examination for a relative afferent pupillary defect to evaluate for possible optic neuropathy.

It's important to document the

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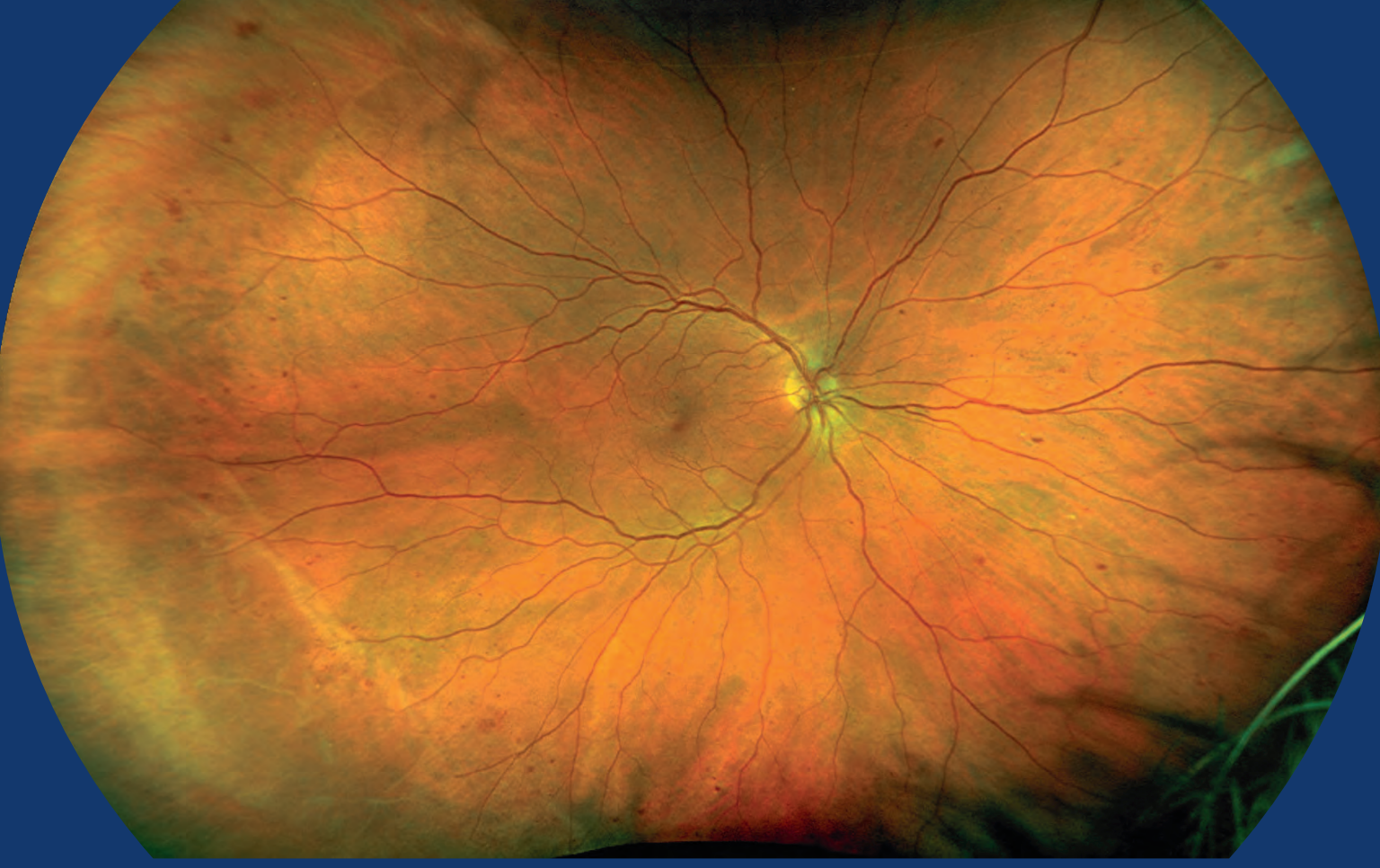
Dr. Regillo is the director of the Retina Service of Wills Eye Hospital, a professor of ophthalmology at Thomas Jefferson University School of Medicine and the principle investigator for numerous major international clinical trials.
Dr. Yonekawa is an assistant professor of ophthalmology at Sidney Kimmel 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.



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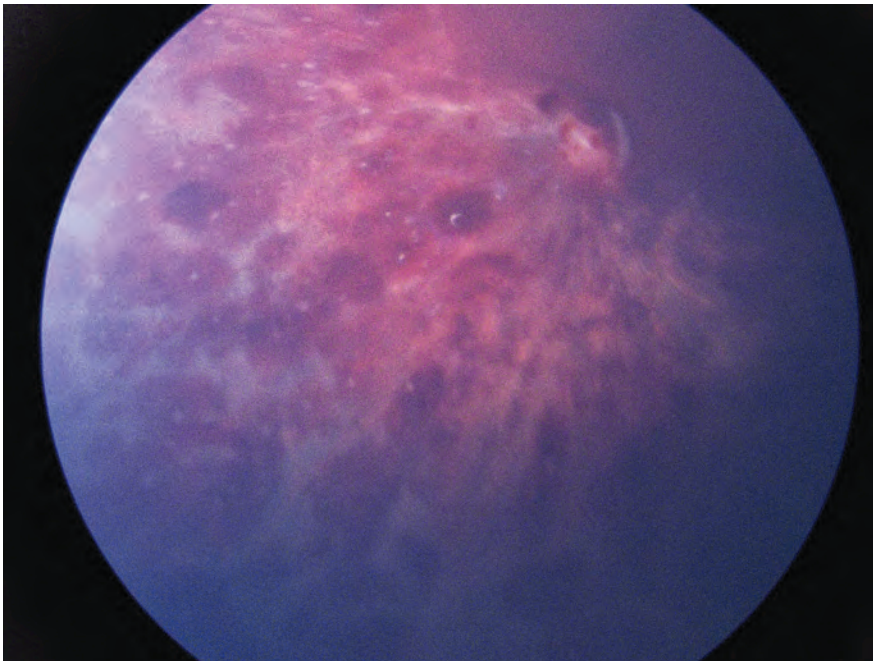

Figure 1. Extensive multilayered retinal hemorrhages in a child with abusive head trauma.

exam findings in detail. When retinal hemorrhages are present, comment on the type (e.g., vitreous, preretinal, intraretinal, subretinal), number, size, location and distribution of the findings. Also note any additional findings, such as perimacular retinal folds or traumatic retinoschisis. In the absence of a clear external source of high-level accidental head trauma, severe findings should raise suspicion for AHT. Fundus photography is highly recommended to document findings.

Intraocular Hemorrhages In AHT

The most common ocular abnormalities seen in AHT are intraocular hemorrhages, seen in around 75 percent of AHT patients *(Figure 1)*. Therefore, intraocular hemorrhage remains the most reliable clinical feature of AHT. Intraocular hemorrhage has been found in children with accidental trauma, such as severe motor vehicle accidents, but hemorrhages from AHT typically occur in a pattern distinctly different from those associated with accidental trauma. Abusive head trauma-induced hemorrhages are typically found in all retinal layers, although they may be confined to the superficial layers (e.g., round or boat-shaped sub-internal limiting membrane hemorrhages, and splinter and flame-shaped nerve fiber and ganglion cell layer hemorrhages).[3] Vitreous hemorrhage and choroidal or sub-retinal pigment epithelial hemorrhage may also be seen. The posterior pole is the most common location for retinal hemorrhages, though more than half of patients have hemorrhages extending to the mid-periphery and peripheral retina. Furthermore, nearly 75 percent of AHT patients with intraocular hemorrhage have bilateral findings.[3]

Intraretinal hemorrhages may resolve over the course of days, whereas preretinal hemorrhages may persist for weeks, thus resulting in rapid evolution of the examination findings, and necessitating examination within 24 for 48 hours of initial presentation in order to document the full extent of injuries.[6] In cases of postmortem evaluation, histological examination may also support the clinical diagnosis of AHT by showing the presence of intraretinal hemorrhages, intrascleral hemorrhages, optic nerve sheath hemorrhages and perimacular folds.

Retinal Folds and Traumatic Retinoschisis

Perimacular or paramacular retinal folds and traumatic retinoschisis are less common than retinal hemorrhages, occurring in approximately 10 percent of AHT cases.[3] As described above, the pathogenesis is thought to be due to intense shearing forces at the vitreoretinal interface. Although the presence of retinal folds or traumatic retinoschisis is not diagnostic of AHT, there are only rare case reports of these findings occurring in patients with alternate mechanisms of head trauma, including fatal motor vehicle accidents and fatal crush injuries.[7-9] It can be challenging to distinguish traumatic retinoschisis from preretinal hemorrhages, as traumatic retinoschisis may sometimes involve only superficial retinal structures (e.g., internal limiting membrane and/or retinal nerve fiber layer), and may be accompanied by hemorrhage into the schisis cavity *(Figure 2A)*. Additionally, there may be overlying vitreous or preretinal hemorrhage obscuring the view. On binocular indirect ophthalmoscopy, traumatic retinoschisis may be identified as an elevation of the internal limiting membrane or other retinal layers that may be bordered by retinal folds or circumlinear hypopigmented lines.[10] Traumatic schisis cavities often don't resolve (*Figure 2B*), and may be accompanied by pre-retinal or subretinal fibrosis, pigmentary changes or macular holes *(Figure 3)*.

Differential Diagnosis

It's important to consider relevant history and physical examination findings, as well as radiologic and laboratory studies, when evaluating the likelihood of AHT. Furthermore, it's possible for more than


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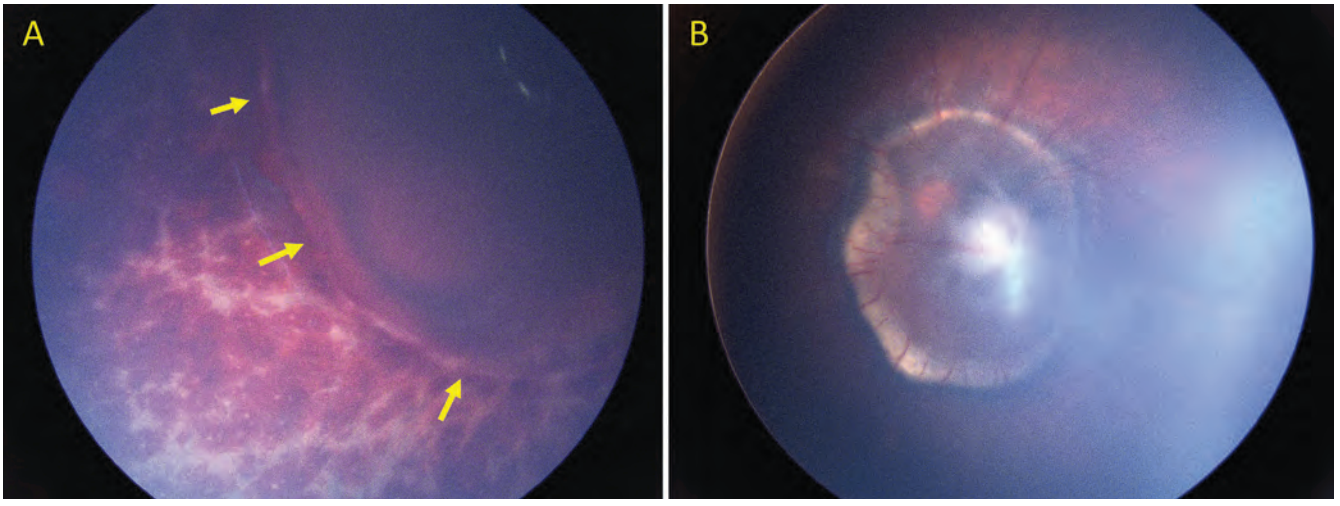

Figure 2. Traumatic retinoschisis in a child with AHT. (A) Acute presentation of AHT with multilayered retinal hemorrhages and traumatic retinoschisis (arrows). Hemorrhage is seen within the schisis cavity. (B) Two years after the injury, the schisis persists and is accompanied by pre-retinal fibrosis and a ring of subretinal fibrosis.

one etiology to contribute to clinical findings, thus the confirmation of an alternate diagnosis shouldn't exclude the possibility of concomitant abusive head trauma.

• ***Accidental head injury.*** Victims of AHT often have limited visible external injuries, whereas in case reports of accidental head injuries resulting in retinal manifestations similar to those seen in AHT there is typically significant external injury. Moreover, in cases of accidental head injury with retinal findings similar to those seen in AHT, the injury is often severe and commonly fatal (e.g., high speed motor vehicle accident or crush injury to head).

• ***Birth trauma.*** Birth-related retinal hemorrhages are common and may be seen in around one-third of newborns and typically resolve within the first month of life. Although there are many clinical features that may be shared between the two entities, birth-related retinal hemorrhages are unlikely to involve vitreous, preretinal, or subretinal hemorrhages, and are unlikely to persist beyond 1 month of age.[11]

• ***Hematologic abnormalities.*** It's important to check laboratory tests to evaluate for hematologic abnormalities in patients with suspected AHT in the absence of other evidence of physical abuse. It's possible for hematologic abnormalities such as coagulopathy (including hemophilia, thrombocytopenia and vitamin K deficiency) or hematologic malignancy to result in intracranial hemorrhage and, less commonly, retinal hemorrhages. Retinal hemorrhages due to hematologic abnormalities are usually less severe than in cases of AHT, and are often confined to the posterior pole. In patients with leukemia, it's possible for the retinal hemorrhages to be more severe, more diffuse and accompanied by white-centered hemorrhages. Hematologic abnormalities aren't associated with retinal folds or retinoschisis, and the presence of those findings should increase suspicion for abusive head trauma.[12]

• ***Intracranial hemorrhage (Terson***

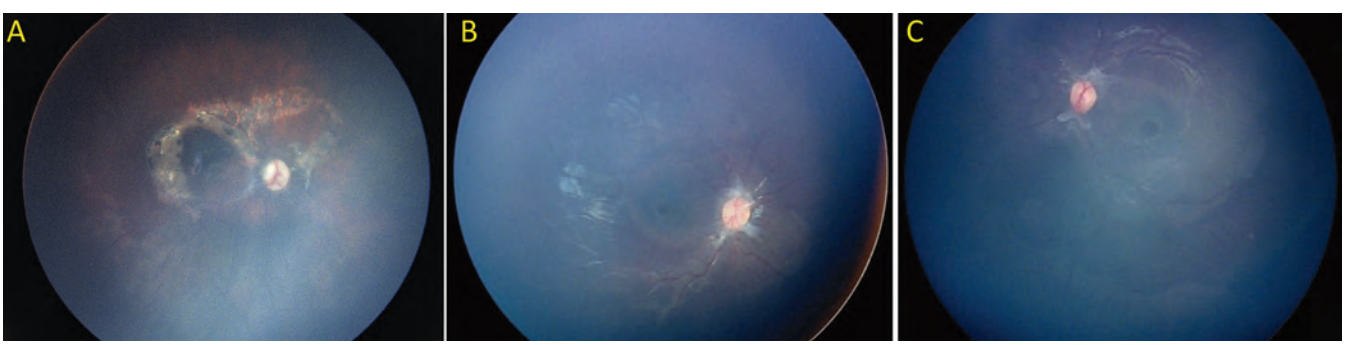

Figure 3. Chronic complications of abusive head trauma. (A) Perimacular subretinal fibrosis and pigmentary changes in a 3-year-old child with a history of AHT. (B-C) Pre-retinal fibrosis and bilateral full thickness macular holes in a 4-year-old child with a history of abusive head trauma.

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Please see Brief Summary on adjacent page and Full Prescribing Information at verkazia.com.

REFERENCES: 1. Verkazia [package insert]. Emeryville, CA: Santen Inc.; 2021. **2.** Leonardi A, Doan S, Amrane M, et al; for VEKTIS Study Group. A randomized, controlled trial of cyclosporine A cationic emulsion in pediatric vernal keratoconjunctivitis: the VEKTIS study. *Ophthalmology*. 2019;126(5):671-681. doi:10.1016/j.ophtha.2018.12.027 **3.** Bremond-Gignac D, Doan S, Amrane M, et al; for VEKTIS Study Group. Twelve-month results of cyclosporine A cationic emulsion in a randomized study in patients with pediatric vernal keratoconjunctivitis. *Am J Ophthalmol*. 2020;212:116-126. doi:10.1016/j.ajo.2019.11.020 **4.** US Department of Health and Human Services. *Orange Book: Approved Drug Products With Therapeutic Equivalence Evaluations*. 42nd ed. US Government Publishing Office; 2022. Accessed March 16, 2022. https://www.fda.gov/media/71474/download

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cyclosporine ophthalmic emulsion 0.1%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Verkazia ophthalmic emulsion (0.1% (1mg/mL) cyclosporine) is indicated for the treatment of vernal keratoconjunctivitis (VKC) in children and adults.

GENERAL DOSING INFORMATION
Contact lenses should be removed before applying Verkazia and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 10 minutes apart to avoid diluting products. Administer Verkazia 10 minutes prior to using any eye ointment, gel or other viscous eye drops.

DOSAGE AND ADMINISTRATION
Instill one drop of Verkazia, 4 times daily (morning, noon, afternoon, and evening) into each affected eye.

Treatment can be discontinued after signs and symptoms are resolved and can be reinitiated if there is a recurrence.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Potential for Eye Injury and Contamination
To avoid the potential for eye injury or contamination, advise patients not to touch the vial tip to the eye or other surfaces.

ADVERSE EVENTS
Table 1: Adverse Reactions Reported in ≥ 1% of Patients Receiving Verkazia

	(N=135)
Eye Disorders	
Eye pain[a]	12%
Eye pruritus[b]	8%
Ocular discomfort[c]	6%
Visual acuity reduced	5%
Ocular hyperemia	4%
Systemic	
Cough	5%
Headache	4%
Upper respiratory tract infection	2%

a Including eye pain and instillation site pain
b Including eye pruritus and instillation site pruritus
c Including foreign body sensation and ocular discomfort

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no adequate and well-controlled studies of Verkazia administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses [*see Data*].

Data
Animal Data
Oral administration of cyclosporine oral solution (USP) to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body weight) were approximately 320 and 2150 times higher than the daily maximum recommended human ophthalmic dose (MRHOD) of 0.015 mg/kg/day, respectively.

No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 185 and 650 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 485 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in mothers or offspring were observed at oral doses of up to 15 mg/kg/day (160 times greater than MRHOD).

Pediatric Use
Verkazia's safety and effectiveness has been established in patients from 4 through 18 years of age.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. The low dose in mice is approximately 5 times greater than MRHOD.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low dose in rats is approximately 5 times greater than MRHOD.

Mutagenesis
In genetic toxicity tests, cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. Cyclosporine was positive in an in vitro sister chromatid exchange (SCE) assay using human lymphocytes.

Impairment of Fertility
Oral administration of cyclosporine to rats for 12 weeks (male) and 2 weeks (female) prior to mating produced no adverse effects on fertility at doses up to 15 mg/kg/day (160 times higher than MRHOD).

CLINICAL STUDIES
The safety and efficacy of Verkazia for the treatment of VKC was evaluated in two randomized, multi-center, double-masked, vehicle-controlled, clinical trials (VEKTIS Study; NCT01751126 and NOVATIVE Study; NCT00328653).

A total of 168 and 118 patients were enrolled in the VEKTIS and NOVATIVE studies for the efficacy analyses, respectively. Patients' age ranged from 4 through 17 years (mean age 9 years) in VEKTIS and 4 through 21 years (mean age 9 years) in NOVATIVE, with most patients being between 4 and 11 years of age (76% in VEKTIS and 80% in NOVATIVE) and male (79% in VEKTIS and 81% in NOVATIVE). Most of the patients had both limbal and tarsal forms of VKC (65% in VEKTIS and 74% in NOVATIVE). In both studies, patients had experienced VKC for a mean of 3 years prior to enrollment and all patients had a history of at least one recurrence of VKC in the year prior to study entry.

STORAGE AND HANDLING
Do not freeze Verkazia. Store at 20°C to 25°C (68°F to 77°F). After opening the aluminum pouch, the single-dose vial should be kept in the pouch to protect from light and avoid evaporation. Any opened individual single-dose vial with any remaining emulsion should be discarded immediately after use.

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DIFFERENTIAL DIAGNOSIS

- Abusive head trauma
- Accidental head injury
- Birth trauma
- Hematologic abnormalities (e.g., coagulopathy, hyperviscosity)
- Intracranial hemorrhage (Terson syndrome)
- Papilledema
- Purtscher retinopathy or resuscitation trauma

syndrome). Intraocular hemorrhage may be associated with intracranial hemorrhage due to vascular abnormality or trauma. Various mechanisms have been proposed to explain the findings, including intracranial blood passing through the optic nerve sheath, or alternatively, acute increase in pressure transmitted through the optic nerve sheath resulting in compression of the central retinal vessels and subsequent microvascular rupture.[13,14] The most common manifestations are vitreous or preretinal hemorrhages, whereas widespread multi-layered or intraretinal hemorrhages as seen in abusive head trauma aren't common.

- ***Papilledema.*** In cases of optic disc edema due to sustained elevation of intracranial pressure, it's possible to see superficial peripapillary hemorrhages (e.g., flame-shaped hemorrhages). The presence of widespread and/or multi-layered retinal hemorrhages isn't consistent with papilledema alone and you should consider alternate or additional diagnoses.
- ***Purtscher retinopathy or resuscitation trauma.*** Purtscher retinopathy may occur in cases of acute severe thoracic compression. It manifests as white retinal lesions (Purtscherflecken) that are caused by infarcts of the retinal nerve fiber layer similar to cotton wool spots, and can be associated with retinal hemorrhages and peripapillary retinal edema. Thoracic trauma including trauma inflicted by chest compressions performed during cardiopulmonary resuscitation don't cause multi-layered retinal hemorrhages such as those seen in cases of abusive head trauma.

Prognosis and Management

The overall prognosis for victims of abusive head trauma is poor, with a reported mortality rate of around 25 percent.[15]

Ocular findings shown to be independent risk factors for increased mortality include poor visual acuity at initial presentation, diminished pupillary response, optic disc edema and diffuse retinal hemorrhages or retinal folds.[16–18] Most survivors of abusive head trauma have long-term neurologic sequelae. Visual prognosis is guarded, and most survivors suffer permanent vision loss in one or both eyes due to brain and/or ocular injuries.[2,19,20] Ocular etiologies of permanent vision loss from abusive head trauma include retinal detachment, macular scarring or fibrosis, and amblyopia

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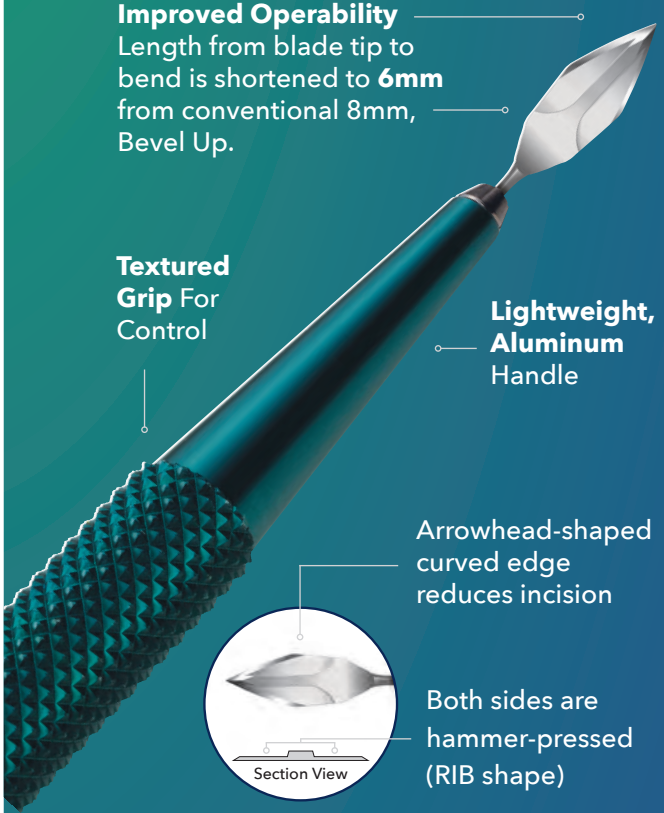

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RETINA RESEARCH UPDATE: STUDY IDENTIFIES UNEVEN TREATMENT PATTERNS FOR DME

Investigators set out to characterize long-term, real-world anti-VEGF treatment patterns in patients with diabetic macular edema, and found that while more than half discontinue intravitreal injections after about six months, one third of them restarted treatments after about 15 months.

Theodore Leng, MD, MS, director of clinical and translational research, Byers Eye Institute at Stanford University School of Medicine, presented results from a retrospective analysis of 190,345 eyes of 147,687 patients in the IRIS Registry from 2015 through 2019.[1] It's the largest known follow-up to date of anti-VEGF treatment patterns for DME, he said.

In any given year, about one-third of patients discontinued anti-VEGF treatments, he said, and 77 percent of eyes received only one anti-VEGF agent over an average follow-up of 2.3 years. Bevacizumab is the most commonly used agent, representing 53 percent of study eyes, followed by aflibercept (21 percent) and ranibizumab (11 percent).

However, many patients switch agents, he noted. "As each year passed, bevacizumab use decreased by a mean 5.6 percent and on-label agent use increased by 6.5 percent," he said. "Fifteen percent of eyes switched during the study period after 53 weeks, of which 74 percent switched from bevacizumab to an on-label agent." Ten percent of eyes did the reverse, switching from an on-label agent to bevacizumab.

The study also found that discontinuation rates were "mostly similar" regardless of baseline vision. "Although," Dr. Leng added, "discontinuation with no re-initiation of injections during follow-up was highest in patients with vision of 20/100 or worse at baseline."

The study data were not robust enough to determine a difference between patients who discontinued treatment and those lost to follow-up for 12 months, Dr. Leng said. And comorbidities that may have influenced treatment patterns weren't captured.

"This is the largest and longest follow-up study known to date, extending out to six years, for evaluating patients with DME in the registry," he said. "The reasons for switching agents should be further explored."

Roche funded the study. Dr. Leng is a consultant to Genentech/Roche and Regeneron.

1. Leng T, Garmo V, Tabano D, et al. Long-term real-world treatment patterns among patients with diabetic macular edema initiating anti-VEGF: 6-year follow-up using the IRIS Registry. Paper presented at the American Society of Retina Specialists annual meeting; July 15, 2022; New York, NY.

associated with non-clearing vitreous hemorrhage. Regular follow-up with an ophthalmologist is needed to maximize visual outcome.

In conclusion, abusive head trauma is a significant cause of morbidity and mortality in infants and children. Diagnosis of AHT requires accurate clinical history, a dilated fundus examination and neuroimaging. Examination by an ophthalmologist is an important part of the evaluation for suspected AHT, as funduscopic examination can reveal findings that have high specificity for AHT. The funduscopic examination should take place within 24 to 48 hours of presentation. Even if pharmacologic pupillary dilation is contraindicated, you should attempt an undilated exam rather than deferring examination. Multiple, bilateral and multi-layered retinal hemorrhages that extend to the periphery of the retina, as well as retinal folds and traumatic retinoschisis are findings that are highly specific for AHT. When possible, perform fundus photography to document your exam findings. If you identify findings suspicious for AHT, notify appropriate child protective services personnel, and arrange for a comprehensive evaluation for additional signs of abuse.

> **Ocular findings shown to be independent risk factors for increased mortality include poor visual acuity at initial presentation, diminished pupillary response, optic disc edema and diffuse retinal hemorrhages or retinal folds.[16–18]**

Prognosis is guarded, unfortunately, due to a high mortality rate and high incidence of long-term visual and neurologic sequelae in survivors. The patient needs to have follow-up ophthalmologic exams to address any reversible causes of vision loss and maximize visual potential. ◀

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None of the authors has any financial interest in any of the products mentioned in the article.

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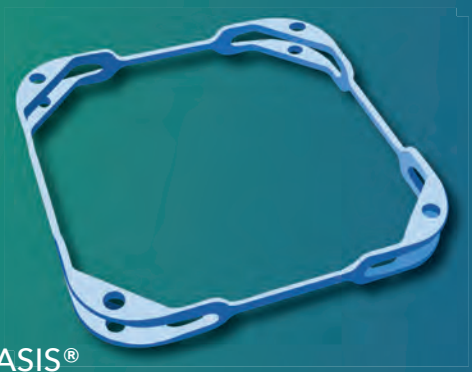

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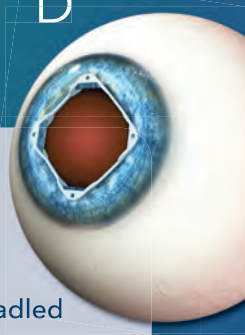

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Detecting Progression in Severe Glaucoma

Observing and measuring change becomes challenging when the disease is advanced. Here's help.

DAVID S. GREENFIELD, MD
MIAMI

Detecting and monitoring progression is a key part of managing glaucoma, but the difficulty of doing this changes as the damage caused by the disease increases. It's particularly challenging to detect changes in eyes with severe glaucomatous damage because there are very few progression endpoints to monitor at that stage. That's especially true in eyes with totally cupped optic nerves, diffuse loss in the visual field and severe atrophy of the retinal nerve fiber layer. However, monitoring progression in eyes with advanced disease is still possible.

A number of considerations are important for clinicians to recognize when trying to detect change in eyes with severe glaucoma. Here, I'll review some of the key issues you may encounter in this situation and offer some suggestions for successful monitoring of the disease, despite the obstacles.

The Floor Effect

To begin, it's important to establish a useful way to define severe glaucoma. For a number of years, clinicians used the Hodapp-Parish-Anderson classification, in which severe disease was defined as having a visual field mean deviation value worse than -12 D of attenuation. However, in 2011, the ICD-10 classification created new glaucoma severity staging codes with a different definition. Severe glaucoma was then defined as either (or both) of two things: having visual field loss in both the superior and inferior hemifields, and/or having visual field loss in the central five degrees. This definition is currently favored by clinicians. (Note that having damage in the central five degrees is much more common than many people realize—particularly in eyes with low-pressure glaucoma, which often develop paracentral scotomas. In the United States, low-pressure glaucoma represents between 30 and 50 percent of all cases of open-angle glaucoma.)

To understand the difficulty of monitoring progression in patients with advanced glaucoma it's important to understand the concept of the floor effect. The "floor" is the level for any given technology below which further disease-related changes become undetectable.

All measurements have a floor effect. In visual fields, when the MD becomes worse than -20 dB, one has typically reached the floor. (Aids to monitoring progression such as GPA generally become useless at this stage.) With SD-OCT imaging, when the average retinal nerve fiber layer thickness reaches between 50 and 60 µm, that's believed to represent the floor. The practical issue here is obvious: Once no further change can be measured, the technology loses its usefulness as a means to monitor worsening of the disease.

Fortunately, even though the visual field mean deviation and average retinal nerve fiber layer measured by OCT may reach a floor, localized changes can still be detected, both with perimetry and OCT imaging. For that reason, it's important to understand that alternative measurements with both technologies should be incorporated when managing these patients. In terms of visual field testing, that usually means testing the central 10 degrees, a very useful strategy for detecting change in eyes with severe glaucoma. A central 10-degree visual field captures 68 points in the center of the visual field, allowing one to continue to detect change over time by analyzing changes in central sensitivity values. In terms of OCT, macular imaging is very useful for detecting structural changes in eyes with severe glaucoma. Furthermore, changes in the central 6 mm of the macula show excellent correlation with changes in the central-10-degree visual field.[1]

Structure vs. Function

Another important consideration to keep in mind when monitoring patients with severe glaucoma is that structural and functional measurements often don't coincide. In 2019 our group published a study in *Ophthalmology Glaucoma*, in which we examined the structure-function relationship in 147 glaucomatous eyes that were followed for a mini-

This article has no commercial sponsorship.

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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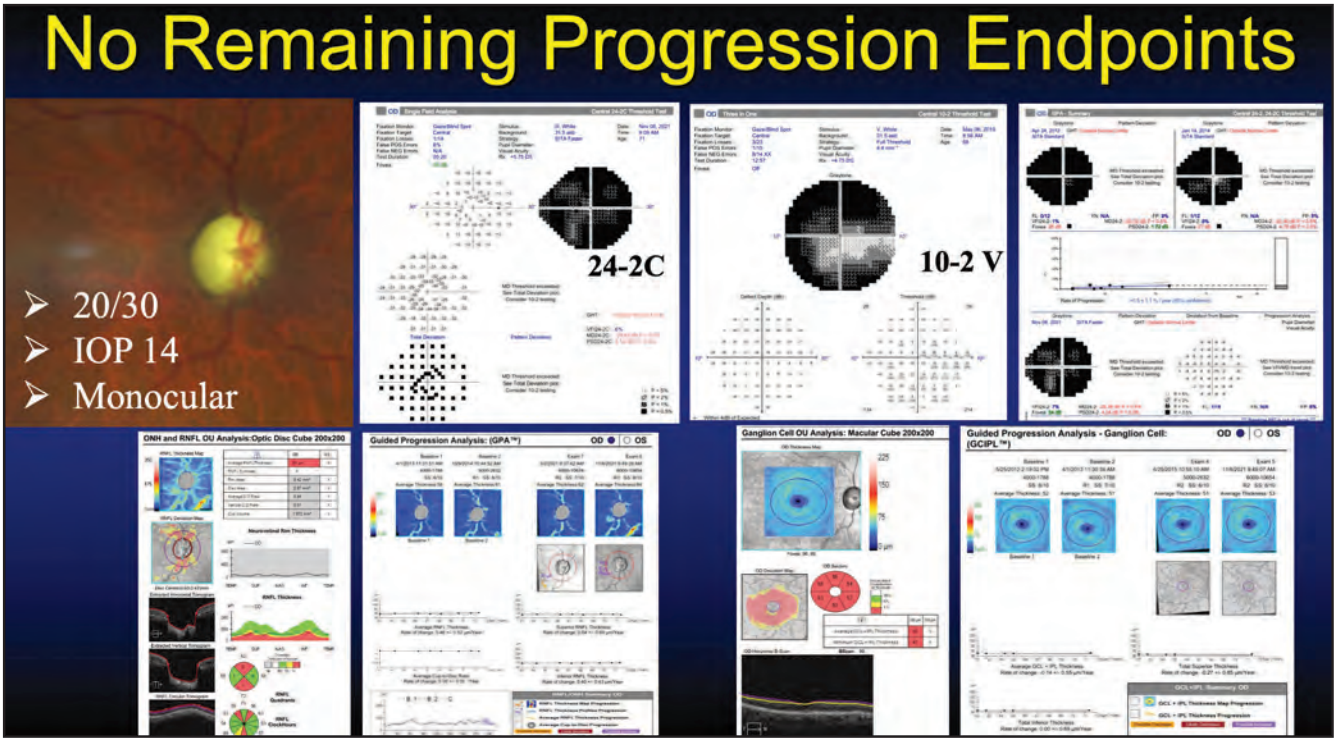

A key challenge when monitoring a patient with advanced glaucoma is that measurements can reach a floor, beyond which it becomes difficult or impossible to detect progression, as in the patient shown above. The nerve is totally cupped, hiding any further change; all visual field parameters have reached the floor; and changes in the nerve fiber and the ganglion cell-inner plexiform layer thicknesses can't be followed beyond this point. In this situation, adding adjunct testing may provide a way to continue monitoring the patient.

mum of three years with serial visual field testing, retinal nerve fiber layer imaging and macular OCT imaging.[2] We found that in eyes with severe glaucoma—as defined by the ICD criteria—there were significantly more OCT progression endpoints than there were visual field progression endpoints. Furthermore, detecting progression using all three modalities in the same eye was uncommon, occurring in approximately 7 percent of eyes.

Typically, one can expect to see either structural progression or functional progression. Methods for progression detection frequently disagree, for a number of reasons. For one thing, the analysis methods used by these technologies differ; for example, regions examined using

DETECTING STRUCTURAL CHANGE IN EYES WITH ADVANCED GLAUCOMA

Despite the floor effect (*see above*) monitoring structural change may still be possible, as the following studies suggest:

— A 2019 study compared the detection and rates of progression in 147 glaucomatous eyes using serial visual fields and SD-OCT imaging of the peripapillary RNFL and macula. There were significantly more OCT progression endpoints than visual field endpoints in eyes with severe glaucoma classified by ICD diagnosis codes.[2]

A number of other studies have also demonstrated that monitoring eyes with advanced glaucoma using SD-OCT is feasible.[4] For example:

— A study from 2016 compared standard SD-OCT structural measures (circumpapillary retinal fiber layer thickness, minimum rim width, and macular retinal ganglion cell-inner plexiform layer thickness) and a new three-dimensional optic nerve head volume measurement (the Bayesian-kernel detection scheme) to see if they could detect progression over time in 35 eyes with advanced glaucoma (defined as visual field mean deviation worse than -21 dB.[5] The study found that both the ganglion cell-inner plexiform layer and Bayesian-kernel detection scheme show promise for identifying change in advanced glaucoma.

— A 2012 study found that monitoring average macular thickness showed promise as a means to detect progression in eyes with advanced glaucoma.[6]

— Another study compared minimum rim width, ganglion cell-inner plexiform layer thickness and circumpapillary retinal nerve fiber layer thickness change in eyes with advanced glaucoma. The researchers found that the GC-IPL thickness stayed above the measurement floor longer than the other measurements, and concluded that GC-IPL measurement is useful for serial monitoring in patients with advanced disease.[7]

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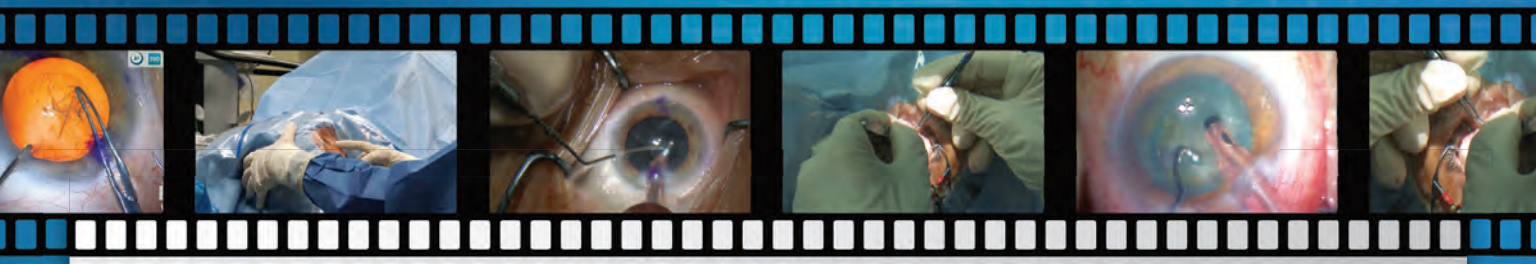

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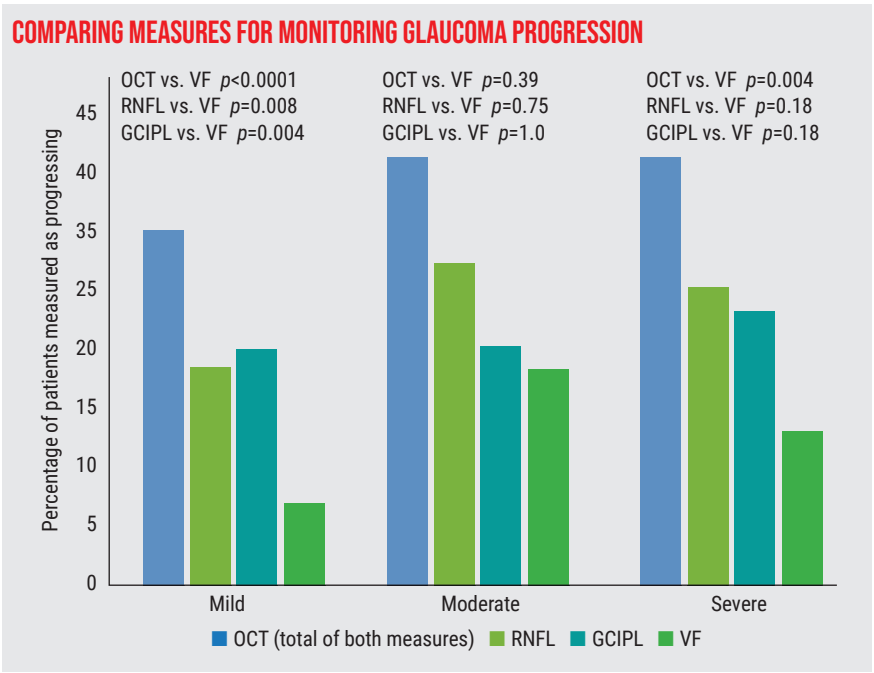
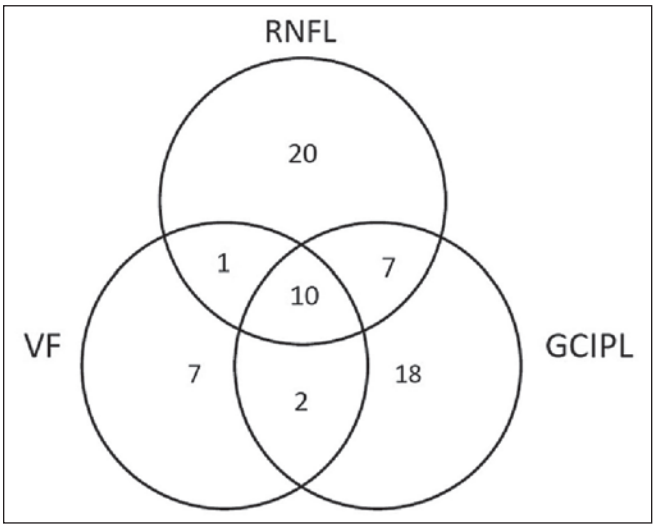


A study compared the detection of progressive loss at three levels of glaucoma severity, using three measures: SD-OCT measurement of the retinal nerve fiber layer and ganglion cell inner plexiform layer, and visual fields.[2] Progression was observed significantly more often using OCT than visual fields in patients with mild or severe disease.

OCT imaging may not correspond to the areas tested by perimetry. There are also differences in the measurement floors with these technologies. In addition, there's a higher prevalence of artifact and variability when measuring eyes with severe glaucoma. That's because the damage in these eyes results in a reduced data signal, both in terms of visual field sensitivity and retinal nerve fiber layer thickness values, causing the algorithms to fail more often.

Another factor that may confound the agreement between measurements is whether you're looking for progression using an event-based strategy or a trend-based strategy. (Trend-based analysis tracks a measurement over time to determine the rate of change; event-based analysis looks at a specific measurement and compares it to a baseline measurement to see whether or not a given change has occurred.) Each of these analysis strategies has strengths and limitations, and while both approaches can be valuable, they've been shown to disagree fairly often.[3]



In the study pertaining to the graph at the top of this page, of the eyes that showed progression in at least one of the three measurements, only 10 eyes showed progression in all three.[2]

Strategies for Success

To be able to continue monitoring a patient with advanced glaucoma, these strategies will help:

• ***Incorporate ancillary diagnostic testing.*** There are a number of options available when looking for progression, and changing the strategy you're using may extend your ability to detect progression despite a significant amount of damage. Central 10-2 visual field testing is essential for serial monitoring in eyes with severe glaucomatous damage. In eyes with extensive visual field loss, using a larger size visual field stimulus (size V) is helpful. In eyes with significant peripapillary RNFL thickness atrophy, where the measurement floor has been reached, performing serial macular OCT imaging to monitor the ganglion cell-inner plexiform layer is recommended.

• ***Perform confirmatory testing.*** Detecting true progression requires confirmatory testing. This is true at all stages of glaucoma severity. Eyes with severe glaucoma have greater variability in test results, particularly in their visual fields, which means you'll encounter more artifacts. Repeated testing can help to compensate for that.

• ***Remember that structural and functional assessments may disagree.*** It's uncommon to see signs of progression using both OCT and visual field testing in an eye with advanced glaucoma.[2] You're more likely to detect progression using one type of testing rather than both. So, if you find evidence of progression on one test, check to make sure it's good-quality data. If the data is reliable and confirmed with repeat testing, it suggests true biological progression.

• ***Use surrogate endpoints for progression.*** In many eyes with severe glaucoma you may find there are no

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CME

CSE GLAUCOMA FELLOWS

Program & Wet Lab

SAVE THE DATE **December 9-10, 2022**

Dear Fellowship Program Director and Coordinator,

We would like to invite you to review the upcoming 2022 Glaucoma Fellowship Program and Wet Lab in Fort Worth at the Renaissance Worthington hotel. The program offers a unique educational opportunity for fellows by providing the chance to meet and exchange ideas with some of the most respected thought leaders in glaucoma. The Glaucoma Fellows Program and Wet Lab is designed to provide your fellows with a state-of-the-art didactic and wet lab experience. The program also serves as an opportunity for your fellows to network with fellows from other programs.

After reviewing the material, it is our hope that you will select and encourage your fellows to attend this educational activity which is CME accredited to ensure fair balance.

Sincerely,
Kuldev Singh, MD

Course Director: Kuldev Singh, MD
Wet Lab Directors & Faculty: To Be Announced

Registration open www.ReviewEdu.com/CSE2022glaucfellows

Participants in this course must be enrolled in a US-based glaucoma fellowship program at the time of the course.
There is no registration fee for these activities. Air, ground transportation in Fort Worth, hotel accommodations and modest meals will be provided through an educational scholarship for qualified participants .

Satisfactory Completion – Learners must complete an evaluation form to receive a certificate of completion. Your chosen sessions must be attended in their entirety. Partial credit of individual sessions is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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more standard progression endpoints to follow. The optic nerve may be totally cupped, the visual field severely depressed and the nerve fiber layer and macular thickness values all at their measurement floor. However, other indicators may still be useful for detecting that the eye is getting worse. These include:

— subjective reporting by the patient, who may describe progressive vision decline or "darkening" of vision;

— a reduction in Snellen visual acuity. You might observe a reduction in central visual acuity over time due to progressive glaucoma;

— optic disc hemorrhages. These have been shown to be one of the most important predictors of progression. Eyes with severe glaucoma develop disc hemorrhages less frequently than eyes with early-to-moderate-stage glaucoma, due to the significant neural atrophy, but their presence is an indicator of ongoing glaucomatous injury. ◀

> **Detecting true progression requires confirmatory testing. Eyes with severe glaucoma have greater variability in test results, particularly in their visual fields, which means you'll encounter more artifacts. Repeated testing can help to compensate for that.**

1. Hood DC, De Moraes GV, Liebmann JM, Ritch R. Glaucomatous damage of the macula. Prog Retin Eye Res 2013;32:1-21.
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7. Bowd C, Zangwill LM, Weinreb RN, et al. Estimating optical coherence tomography structural measurement floors to improve detection of progression in advanced glaucoma. Am J Ophthalmol 2017;175:37-44.

ABOUT THE AUTHOR

Dr. Greenfield is the Douglas R. Anderson Distinguished Chair in Ophthalmology, a professor of ophthalmology and vice-chair for academic affairs at the Bascom Palmer Eye Institute, University of Miami.

(Continued from p. 72)

Premium IOL Practice

great outcomes. So, choose a patient who's an ideal candidate and don't try to stretch into any gray zones."

• ***Follow your results.*** "Creating a personal nomogram and analyzing your results is really important," says Dr. Donaldson. "If a patient has a complication or needs an enhancement, and you're not following your own postoperative outcomes, it can be difficult to know the side effects or what the full patient experience is unless you're closely following your own patient results.

"Track your results and analyze the patient experience throughout the whole process," she says. "The process begins preoperatively and extends through surgery and the postoperative course. Presbyopia-correcting lenses can have some limitations and need enhancements much more frequently than standard distance lenses. Our job doesn't end at the end of the surgery. In fact, a lot of times, that's just the beginning. Some of these patients may take six months to neuro-adapt. Sometimes we may be waiting a few months because we want to do a refractive enhancement, but the patient isn't stable yet. The postop process can be lengthy with premium lens technology.

"We also tend to do Nd:YAG lasers more frequently in our multifocal-lens patients than in our standard-lens patients because they're much more sensitive to small opacities and any small degree of ocular surface disease," she continues. "This may require extended amounts of time preoperatively and postoperatively to manage their ocular surface disease, more so than with a standard-lens patient."

Dr. Khandelwal adds that it's important to educate your technicians about the type of work-up necessary for premium lens patients. "Cataract surgeons need to know their outcomes with different lenses," she says. "If all your technicians are doing for patients with astigmatism- or presbyopia-correcting lenses is checking their visual acuity and not refracting them, you're not going to know what your individual refractive targets are. That's very important with these lenses. We educate our technicians, even our float technicians, that when a patient has a premium lens, they need to check distance, intermediate and near vision, and look for any astigmatism, because these can all affect outcomes. Tracking your outcomes allows you to become a better surgeon because you know what your refractive outcomes are for your cases with these particular lenses." ◀

Results of SEE Glaucoma Coaching Program

Researchers assessed the efficacy of the Support, Educate, Empower (SEE) glaucoma coaching program for medication adherence among poorly adherent glaucoma patients over 12 months following cessation of the intervention, as part of an uncontrolled intervention study with a pre/post design.

The SEE cohort was recruited from the University of Michigan and included glaucoma patients 40 years old and older who were taking at least one medication and self-reporting poor adherence. Electronic medication monitoring of those who completed the program continued for up to one year post-coaching intervention.

Adherence, monitored electronically during the seven- and 12-month follow-up periods, was defined as the percentage of doses taken on time. Participants were censored for surgery, change in glaucoma medications or adherence monitor disuse. The SEE program included automated medication reminders, three motivational counseling sessions with a glaucoma coach and five phone calls with the coach for between-session support, followed by no contact between the study team and participants during the 12-month post-program follow-up. Baseline participant characteristics were summarized with descriptive statistics. Paired T tests and Wilcoxon signed rank tests were used to investigate significant changes in monthly adherence during follow-up.

The main outcome measure was a change in electronically monitored medication adherence over the 12 months following the conclusion of the SEE program.

Here are some of the findings:

- Of 48 participants, 39 (81 percent) completed the SEE program and continued electronic medication monitoring for up to one year after program cessation.
- Participants were on average age 64 (SD: 10); 56 percent were male, with 49 percent black and 44 percent white.
- The average length of follow-up was 284 days (SD: 110; range: 41 to 365 days).
- Censoring occurred in 18 participants (56 percent).
- Average adherence during the follow-up period was 67 percent (SD: 22 percent), which was significantly lower than adherence during the SEE program (mean: 81 percent, SD: 18 percent; $p<0.0001$), but significantly higher than baseline pre-program adherence (mean: 60 percent, SD: 18 percent; $p=0.0393$).
- The largest monthly losses occurred at months one (mean: 7 percent; $p=0.0001$) and four (mean: 6 percent; $p=0.0077$).

Researchers concluded that glaucoma medication adherence decreased significantly in the year after cessation of the SEE coaching program but remained significantly higher than baseline. They suggested that intermittent reinforcement sessions may be necessary to maintain excellent long-term medication adherence.

Ophthalmol Glaucoma 2022; Aug 8. [Epub ahead of print]
Killeen OJ, Niziol LM, Cho J, et al

DR Telemedicine Outcomes with AI-based Image Analysis

Researchers examined real-world telemedicine outcomes of diabetic retinopathy screening with artificial intelligence-based image analysis, reflex dilation and secondary image overread in a primary care setting.

The screening test validity and reliability analysis included single institution review of 1,052 consecutive adult patients who received diabetic retinopathy photoscreening in the primary care setting over an 18-month period. Nonmydriatic fundus photographs were acquired and analyzed by the IDx-DR AI-based system. When nonmydriatic images were ungradable, reflex dilation (1% tropicamide) and mydriatic photography were performed for repeat AI-based analysis. Manual overread was performed on all images. Researchers recorded patient demographics, clinical characteristics and screening outcomes.

Here are some of the findings:

- 91.7 percent (965/1,052) of patients had AI-gradable fundus photographs.
- 55.1 percent (580/1052) of patients had gradable nonmydriatic imaging and 93.2 percent (440/472) with ungradable nonmydriatic photographs had reflex dilation.
- 14.3 percent (138/965) of patients were AI-graded as "positive" (>mild NPDR) and 85.7 percent were graded as "negative" (827/965), with 100-percent sensitivity (CI, 90.8 to 100 percent), 89.2-percent specificity (CI,

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87 to 91.1 percent), 27.5 percent positive predictive value (CI, 24 to 31.4 percent) and 100 percent negative predictive value (CI, 99.6 to 100 percent) vs. manual overread assessment of >mild NPDR requiring further evaluation with a comprehensive dilated exam.

• Image gradeability was inversely related to patient age: images were 93.5 percent gradable (61.9 percent nonmydriatic) for patients ages <70 years vs. 85.3 percent gradable (31 percent nonmydriatic) for patients ages 70-plus (p<0.001).

Researchers determined the addition of AI-based image analysis into real-world primary care diabetic retinopathy screening yielded no false-negative results and offered excellent image gradeability within a protocol that combined nonmydriatic fundus photography and pharmacologic dilation as needed. They also found image gradeability was lower with increasing patient age.

Am J Ophthalmol 2022; Aug 12. [Epub ahead of print].
Mehra AA, Softing A, Kabaalioglu Guner M, et al.

Refractive Surgery in Children

As amblyopia is often caused by uncorrected refractive error, laser vision correction has been suggested in some studies as a viable alternative to expensive and difficult traditional therapies. Based on a literature review, the American Academy of Ophthalmology stated in a recently published technology assessment that laser vision correction appears to address amblyopic refractive error and decrease anisometropia in children.

The researchers conducted a literature review of LASIK, PRK, LASEK and SMILE using the PubMed database and identified 137 articles. A total of 12 studies met inclusion criteria (all level III evidence; two case-control studies and 10 case series). Subjects, aged ≤18, had anisometropic myopia, anisometropic hyperopia or were mixed.

The group reported that all studies demonstrated an improvement in BCVA but that the magnitude of improvement varied. Successful outcomes ranged from 27 percent to 89 percent (residual refractive error within 1 D of target). Mean follow-up ranged from four months to seven years. The researchers noted the wide range but wrote that all studies still showed an improvement in the magnitude of anisometropia. They added that regression in refractive error was more common and occurred to a greater degree in myopic eyes, eyes with longer follow-up and younger patients. Common complications included corneal haze and striae.

While direct comparisons weren't feasible due to differences in methodology, refractive error parameters and outcome measures, the group concluded that their findings suggest laser refractive surgery "may address amblyogenic refractive error in children and that it appears to decrease anisometropia." They noted, however, that the evidence for amblyopia improvement is unclear and there isn't any long-term safety data. Using laser refractive surgery in children has its own challenges, such as the potential need for general anesthesia, and doesn't necessarily obviate the need for glasses, contact lenses or continued amblyopia therapy.

Ophthalmology. 2022;1-9.
Cavuoto KM, Chang MY, Heidary G, et al.

VF Defects in Preperimetric Glaucoma Eyes

Researchers evaluated whether baseline vessel density parameters derived from optical coherence tomography angiography were associated with development of glaucomatous visual field defects in preperimetric glaucoma (PPG) patients.

They retrospectively analyzed one eye from each of 200 consecutive PPG patients with normal standard automated perimetry and optical coherence tomography angiography at baseline. OCTA was used to measure the circumpapillary vessel density and parafoveal and perifoveal vessel density. Researchers measured retinal nerve fiber layer and macular ganglion cell inner plexiform layer thicknesses as reference standards. They stratified two patient groups based on development of repeatable glaucomatous visual field loss and constructed a Cox proportional hazards model to determine the ability of OCTA parameters to predict visual field defects. Researchers calculated correlation between these baseline OCTA parameters and the rate of global visual field sensitivity loss (dB/year) using linear regression analysis.

Here are some of the findings:

• During a 3.1-year average follow-up period, 18 eyes (9 percent) developed glaucomatous VF defects.

• At baseline, the lower inferior temporal circumpapillary vessel density (HR: 0.934; CI, 0.883 to 0.988; p=0.017) and thinner inferior RNFL (HR: 0.895; CI, 0.839 to 0.956; p=0.001) were predictive of glaucomatous VF loss.

• A lower inferior temporal circumpapillary vessel density and thinner RNFL at baseline were associated with faster rates of global VF sensitivity loss (β=0.015; p=0.001).

Researchers found, in PPG eyes, a lower baseline inferior temporal circumpapillary vessel density was significantly associated with glaucomatous VF defect development and faster rate of global VF loss. ◀

Br J Ophthalmol 2022; Aug 5. [Epub ahead of print].
Lee JY, Shin JW, Lee A, et al.

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Course Director
REGISTER NOW

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Zaina Al-Mohtaseb, MD
Course Director
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FEBRUARY 25-26, 2022
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Jonathan Rubenstein, MD
Course Director
REGISTER NOW

Dear Resident Program Director and Coordinator,

We would like to invite you to review the upcoming 2nd-Year Ophthalmology Resident Wet Lab Programs for the 2022-2023 Residency Year in Fort Worth. These programs offer a unique educational opportunity for second-year residents. To better familiarize beginning ophthalmologists with cataract surgery, these programs will consist of both didactic lectures and a state-of-the-art, hands-on wet lab experience. Technology and technique will be explained and demonstrated and surgeons will leave better prepared to optimize outcomes and manage complications when they arise. The programs also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your 2nd Year residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

Sincerely,
Drs. Al-Mohtaseb, DelMonte & Rubenstein

Registration open www.ReviewEdu.com/CSE2ndYr2022-23

CME courses are restricted to 2nd-year residents enrolled in an ophthalmology residency program at the time of the course. There is no registration fee for this activity. Air, ground transportation in Forth Worth, hotel accommodations, and modest meals will be provided through an educational scholarship for qualified participants.

Physicians
In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Review Education Group, LLC. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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A man presents with a vitreous hemorrhage that warrants further investigation.

THEODORE BOWE, MD, RALPH C. EAGLE JR, MD, TATYANA MILMAN, MD, YOSHIHIRO YONEKAWA, MD, AND CAROL L. SHIELDS, MD
PHILADELPHIA

Presentation

A 76-year-old white man presented to his ophthalmologist with sudden decreased vision in the right eye, which occurred two months prior and had not improved.

Medical History

The patient had a central retinal vein occlusion in the left eye in 2020. He denied other past ocular history. Past medical history included coronary artery disease, hypertension, hyperlipidemia and actinic keratosis. Family history was non-contributory. The patient had a history of tobacco smoking and drank alcohol socially. Current medications included atorvastatin 40 mg daily and aspirin 81 mg daily.

Examination

On examination, visual acuity was hand motions OD and 20/60 OS, with intraocular pressures of 20 mmHg OD and 14 mmHg OS. There was no afferent pupillary defect. The external examination was notable for prominent scleral and iris melanocytosis OD, and moderate nuclear sclerotic cataract in each eye *(Figures 1-3)*. View of the right fundus was obscured by vitreous hemorrhage. The left fundus examination was notable for chronic vascular changes consistent with an old central retinal vein occlusion.

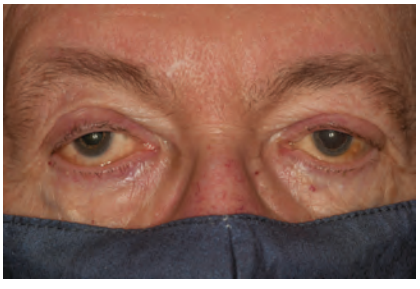


Figure 1. External photograph. Hyperchromic heterochromia of the right eye.

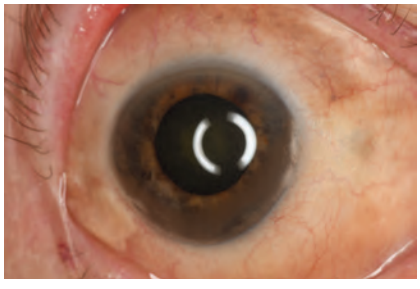


Figure 2. External photograph of the affected right eye. Gray-brown scleral melanocytosis was suggestive of ocular melanocytosis with heterochromia.

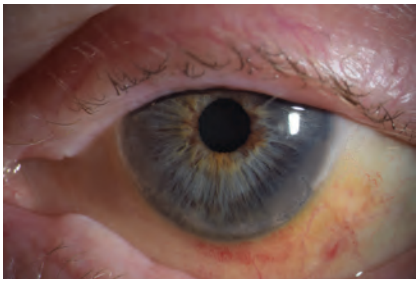
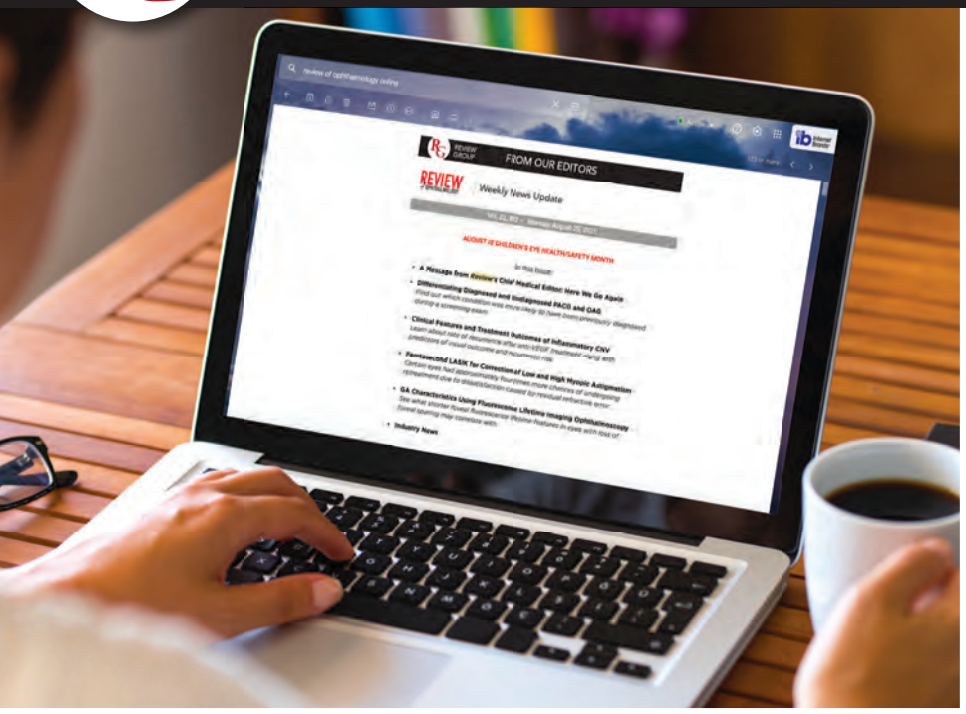


Figure 3. External photograph of the unaffected left eye. Normal iris anatomy and topography and absence of episcleral pigment.

What's your diagnosis? What further work-up would you pursue? The diagnosis appears on p. 96.

REVIEW GROUP / **WEEKLY E-NEWSLETTERS**



Read the Latest from our Editors

FROM OUR EDITORS

Weekly News Update

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

AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

- **A Message from *Review*'s Chief Medical Editor: Here We Go Again**
- **Differentiating Diagnosed and Undiagnosed PACG and OAG**
  Find out which condition was more likely to have been previously diagnosed during a screening exam.
- **Clinical Features and Treatment Outcomes of Inflammatory CNV**
  Learn about rate of recurrence after anti-VEGF treatment along with predictors of visual outcome and recurrence risk.
- **Femtosecond LASIK for Correction of Low and High Myopic Astigmatism**
  Certain eyes had approximately four times more chances of undergoing retreatment due to dissatisfaction caused by residual refractive error.
- **GA Characteristics Using Fluorescence Lifetime Imaging Ophthalmoscopy**
  See what shorter foveal fluorescence lifetime features in eyes with loss of foveal sparing may correlate with.
- **Industry News**

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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Work-up, Diagnosis and Treatment

Ultrasonography OS revealed vitreous debris, suggestive of blood, and serous retinal detachment overlying an intraocular mushroom-shaped mass measuring approximately 11 mm in the largest basal diameter and 8 mm in thickness *(Figure 4)*. These findings were suggestive of uveal melanoma. A vitrectomy was performed to clear the view for intraocular tumor assessment and possible plaque placement. Vitreous cytology revealed chronic vitreous hemorrhage that contained malignant cells *(Figures 5, 6)*. Magnetic resonance imaging (MRI) disclosed an intraocular mass with extrascleral extension *(Figure 7)* and enucleation was recommended. Histopathology of the enucleated eye showed choroidal melanoma with extraocular extension arising in ocular melanocytosis. Additionally, a second melanocytic nodule was noted in the iris, interpreted as an atypical iris tumor *(Figures 8-11)*.

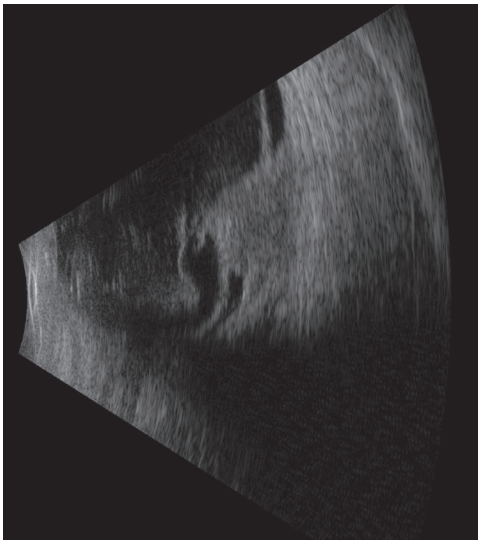

Figure 4. Ultrasound of the right eye revealing an exudative retinal detachment, vitreous hemorrhage and a mushroom-shaped, centrally echolucent choroidal mass, concerning for uveal melanoma.

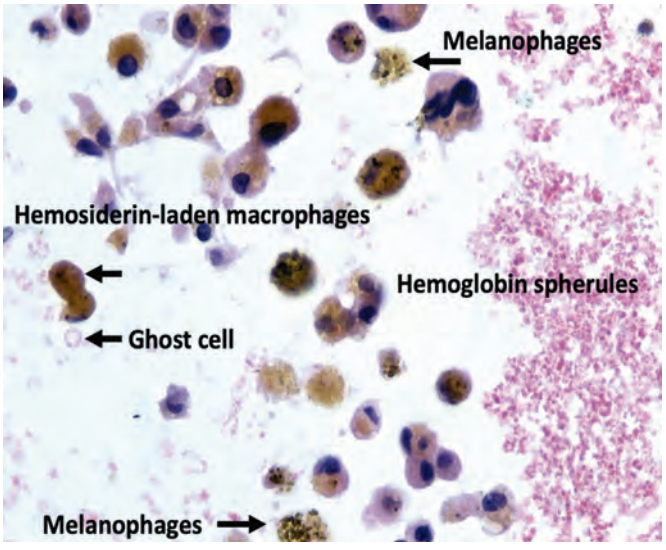

Figure 5. Cytology of the vitreous biopsy, highlighting features consistent with chronic vitreous hemorrhage

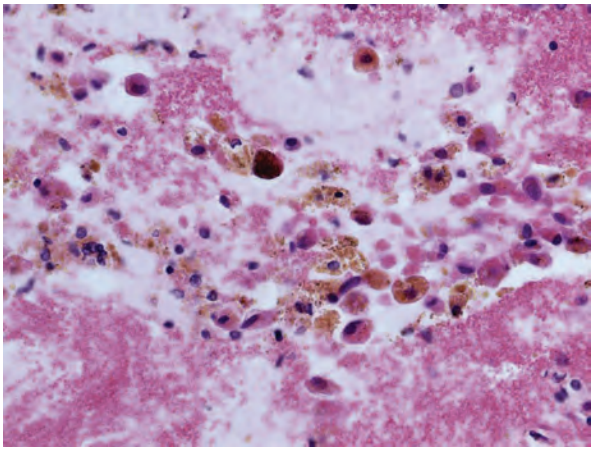

Figure 6. Cytology of the vitreous biopsy, highlighting features consistent with chronic vitreous hemorrhage.

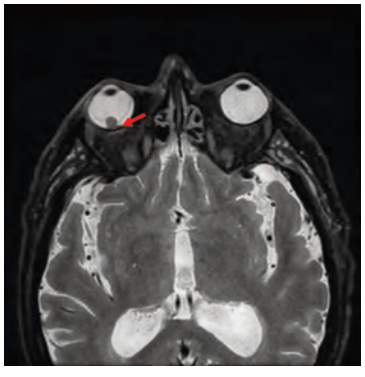

Figure 7. T2 MRI suggesting extrascleral extension of the choroidal mass (arrow).

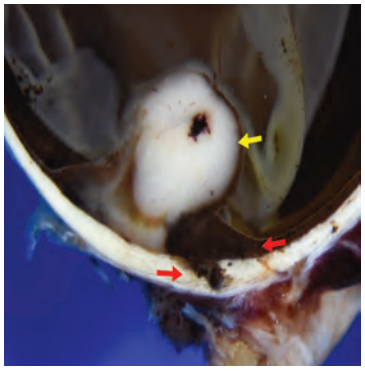

Figure 8. Gross photography of the enucleated specimen. Amelanotic melanoma nodule in a background of a darkly pigmented precursor lesion in the adjacent choroid (yellow arrow). Involvement by melanocytosis of the scleral emissarial canals is also seen (red arrow).

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Rick Bay served as the publisher of *The Review Group* for more than 20 years. To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.

To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

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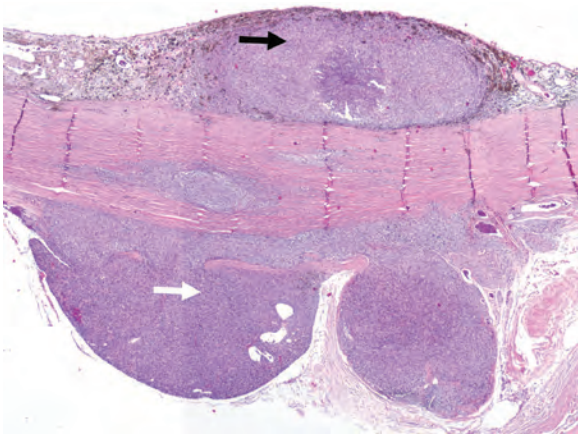

Figure 9. Amelanotic choroidal melanoma nodule (black arrow) with extraocular extension (white arrow).

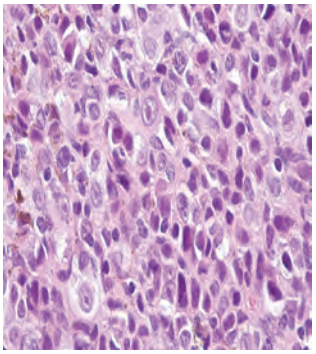

Figure 10. The tumor is composed of pleomorphic epithelioid melanoma cells.

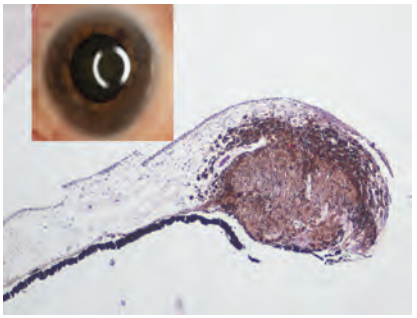

Figure 11. A distinct nodule of darkly pigmented melanocytes in association with a superficial plaque of less pigmented melanocytes on the surface of the iris is visible.

Discussion

Congenital ocular melanocytosis is defined as a congenital nevus composed of dendritic melanocytes involving ocular tissues, including the sclera, episclera and uvea.[1] The condition is called oculodermal melanocytosis or the Nevus of Ota if the tissues of the periocular skin and orbit are involved. Congenital ocular melanocytosis affects less than 1 percent of the Caucasian population and is bilateral in 10 percent of cases.[1] It's been hypothesized that ocular melanocytosis is caused by the arrest or abnormal migration of neural crest-derived melanocytes to the eyelid, orbit and uvea, rather than to the dermoepidermal junction.[3] Histopathologically, ocular melanocytosis is characterized by the proliferation of intensely pigmented dendritic melanocytes in the affected tissue.[1,3] *GNAQ* and *GNA11* mutations have been identified in ocular melanocytosis, conventional uveal tract nevi, uveal melanocytoma and uveal melanoma, indicating that *GNAQ* and *GNA11* mutations are likely an initiating event in the pathogenesis of these melanocytic conditions.

The lifetime risk in Caucasians for the development of uveal melanoma in a setting of ocular melanocytosis is approximately 1 in 400.[1,2] A large study of 7,872 patients with uveal melanoma revealed associated oculodermal melanocytosis in 3 percent of them.[4] Oculodermal melanocytosis not only increases the risk for uveal melanoma, but it also increases the relative risk of metastasis (1.6 times as compared to those with no melanocytosis).[4] This relative risk was greatest among patients with melanocytosis involving the iris (RR 2.8), choroid (RR 2.6) and sclera (RR 1.9).[4] Metastases of uveal melanoma arising in ocular melanocytosis carry a less favorable prognosis than metastasis from uveal melanoma without associated ocular melanocytosis.[4,5] Thus, screening ophthalmologic examinations of patients with ocular melanocytosis at risk for uveal melanoma are recommended every six months.

In summary, vitreous hemorrhage was the presenting manifestation of uveal melanoma in this patient. The incidence of vitreous hemorrhage is seven cases per 100,000.[6] There's a broad differential for vitreous hemorrhage. Common causes include hemorrhagic posterior vitreous or retinal detachment, diabetic eye disease, trauma and vascular occlusive disease. Although less frequent, vitreous hemorrhage can be associated with posterior uveal melanoma, but is relatively uncommon.[7]

Generally, vitreous hemorrhage occurs in a subset of melanomas that have broken through Bruch's membrane and perforated the overlying retina. Retinal perforation is more likely to occur when choroidal tumors originate where the retina and choroid normally are adherent, such as at the ora serrata or the peripapillary choroid. This case highlights the importance of periodic monitoring of patients with ocular melanocytosis for development of uveal melanoma and emphasizes that intraocular tumor should be included in the differential diagnosis of vitreous hemorrhage. Intraocular tumor must be considered in all cases of vitreous hemorrhage, and excluded with a careful history, examination and ultrasonography. ◀

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