Wills Eye Resident Series: Eye pain and photophobia after combined cataract/MIGS, *p. 70*

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RETINAL INSIDER
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AGE (YEARS)

29 30 31

Unlock the Secrets To Better

Covering the spectrum of

Lid Hygiene

The comprehensive iVIZIA product line includes these eyelid hygiene products:

iVIZIA Eyelid Cleansing Wipes—convenient daily cleansing for sensitive eyelids

iVIZIA Micellar Eyelid Cleanser—economical daily cleansing with a micellar formulation

*Prescription market data, Dec. 2022 – S01K without cyclosporine.
†In a chronic dry eye patient usage study, participants from a variety of socioeconomic backgrounds answered questions about their experience with iVIZIA lubricant drops. In the study, 203 chronic dry eye patients, 28-80 years old, switched from their dry eye artificial tears to iVIZIA for a month.[1]
‡To limit blurriness when using contact lenses, remove contacts, apply drops, then insert contacts.

Reference: 1. Thea Data on File.

Théa
let's open our eyes

Wills Eye Resident Series: Eye pain and photophobia after combined cataract/MIGS, *p. 70*

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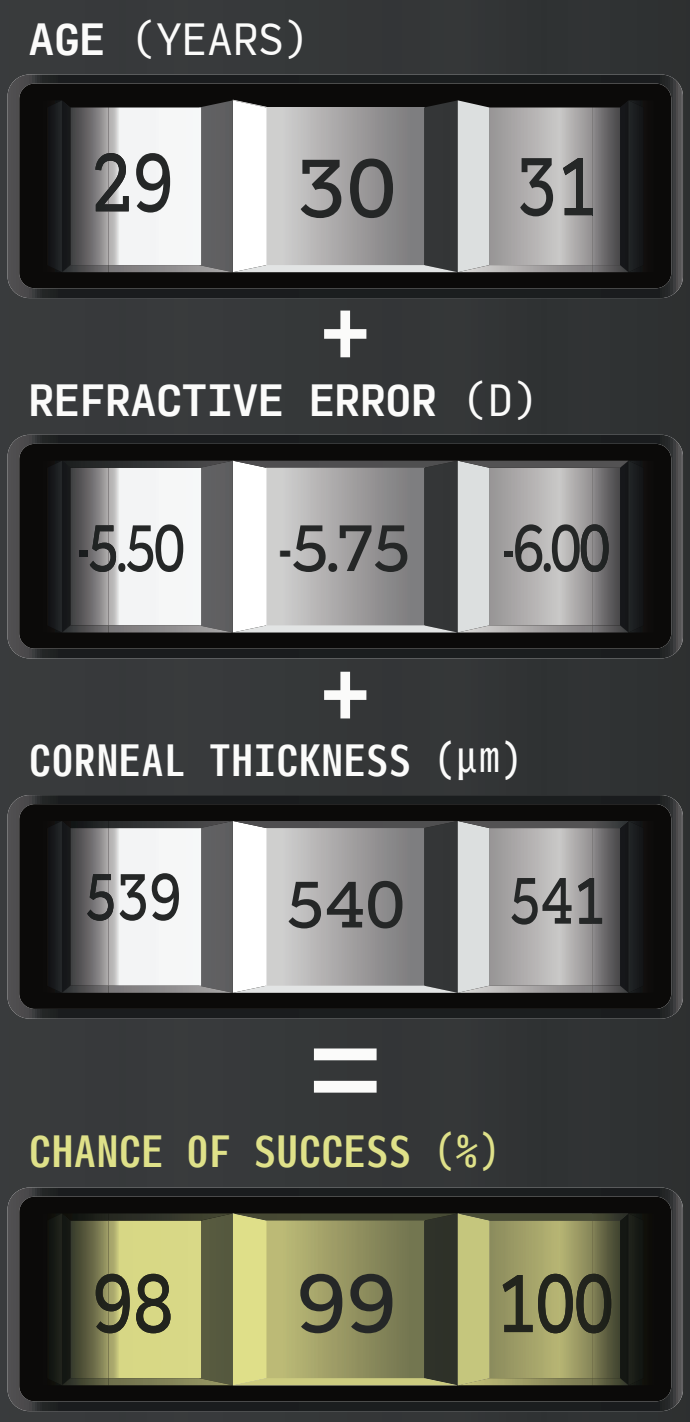

Unlock the Secrets To Better Nomograms

Refractive surgeons detail the ways you can tweak your calculations to get better outcomes. **P. 52**

Also inside:

- Treating Floaters: Pros, Cons and Techniques **P. 29**
- A Closer Look at Same-day Surgery **P. 33**
- Mastering New-technology Lenses **P. 37**
- What's on the Horizon for Keratoconus **P. 46**

Indicated for the treatment of the signs and symptoms of DED

MIEBO is the first and only Rx eye drop for DED that directly targets evaporation[1]

Inhibits tear evaporation[1-3]*

- Forms a monolayer at the air-liquid interface of the tear film which can be expected to reduce evaporation

Rapid and sustained relief[1]†

- Improvement in tCFS and eye dryness as early as Day 15 continued through Day 57 in 2 pivotal studies

Excellent tolerability[1,4-6]‡

- Low rate of burning or stinging on instillation
- Blurred vision and conjunctival redness were reported in 1%-3% of individuals

***The exact mechanism of action for MIEBO in DED is not known.[1]**

†**Study design:** Two 57-day, multicenter, double-masked, saline-controlled studies (GOBI and MOJAVE) were conducted in adults ≥18 years old with a self-reported history of DED in both eyes. Across GOBI and MOJAVE, 614 patients received MIEBO and 603 patients received control with 591 and 575, respectively, assessed on Day 57. **Primary endpoints were change from baseline in tCFS and change from baseline in eye dryness score at Day 57.** Day 15 was the earliest time point at which signs and symptoms were evaluated in the trials. Day 57 was the last.[1,5,6]

‡In 2 pivotal studies of >1200 patients (614 patients received MIEBO), there were no incidences of serious ocular AEs with MIEBO. Most AEs were considered mild. The discontinuation rate for MIEBO was comparable to control (pooled: 0.2% vs 0.5%; GOBI: 0.3% vs 1.0%; MOJAVE: 0% vs 0%). 0.5% (pooled) of patients experienced instillation site pain AEs, such as burning or stinging (GOBI: 1.0%; MOJAVE: 0%). Blurred vision (pooled: 2.1%; GOBI: 3.0%; MOJAVE: 1.3%) and conjunctival redness (pooled: 0.8%; GOBI: 0%; MOJAVE: 1.3%) were reported in 1%-3% of individuals.[1,4-6]

AE, adverse event; DED, dry eye disease; tCFS, total corneal fluorescein staining.

INDICATION

MIEBO™ (perfluorohexyloctane ophthalmic solution) is a semifluorinated alkane indicated for the treatment of the signs and symptoms of dry eye disease.

IMPORTANT SAFETY INFORMATION

- MIEBO should not be administered while wearing contact lenses. Contact lenses should be removed before use and for at least 30 minutes after administration of MIEBO
- Instruct patients to instill one drop of MIEBO into each eye four times daily
- The safety and efficacy in pediatric patients below the age of 18 have not been established
- The most common ocular adverse reaction was blurred vision (1% to 3% of patients reported blurred vision and conjunctival redness)

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying Brief Summary of full Prescribing Information for MIEBO.

References: 1. MIEBO. Prescribing Information. Bausch & Lomb, Inc; 2023. **2.** Sheppard JD, Nichols KK. Dry eye disease associated with meibomian gland dysfunction: focus on tear film characteristics and the therapeutic landscape. *Ophthalmol Ther*. 2023;12(3):1397-1418. doi:10.1007/s40123-023-00669-1 **3.** Vittitow J, Kissling R, DeCory H, Borchman D. In vitro inhibition of evaporation with perfluorohexyloctane, an eye drop for dry eye disease. *Curr Ther Res Clin Exp.* 2023;98:100704. doi:10.1016/j.curtheres.2023.100704 **4.** Data on file. Bausch & Lomb, Inc; 2023. **5.** Tauber J, Berdy GJ, Wirta DL, Krösser S, Vittitow JL; GOBI Study Group. NOV03 for dry eye disease associated with meibomian gland dysfunction: results of the randomized phase 3 GOBI study. *Ophthalmology*. 2023;130(5):516-524. doi:10.1016/j.ophtha.2022.12.021 **6.** Sheppard JD, Kurata F, Epitropoulos AT, Krösser S, Vittitow JL; MOJAVE Study Group. NOV03 for signs and symptoms of dry eye disease associated with meibomian gland dysfunction: the randomized phase 3 MOJAVE study. *Am J Ophthalmol*. 2023;252:265-274. doi:10.1016/j.ajo.2023.03.008

BAUSCH + LOMB

MBO.0098.USA.23 V2.0

Learn more at MIEBO-ECP.COM

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use MIEBO safely and effectively. See full Prescribing Information for MIEBO.

MIEBO™ (perfluorohexyloctane ophthalmic solution), for topical ophthalmic use

Initial U.S. Approval: 2023

1 INDICATIONS AND USAGE

MIEBO™ (perfluorohexyloctane ophthalmic solution) is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

MIEBO should not be administered while wearing contact lenses. Advise patients that contact lenses should be removed prior to and for at least 30 minutes after administration of MIEBO.

6 ADVERSE REACTIONS

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 patients with DED, 614 patients received at least one dose of MIEBO in two randomized controlled clinical trials across 68 sites in the United States. The most common ocular adverse reaction was blurred vision. Blurred vision and conjunctival redness were reported in 1-3% of individuals.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well controlled studies with MIEBO in pregnant women.

In animal reproduction studies with oral administration of perfluorohexyloctane during the period of organogenesis, no adverse maternal or developmental effects were observed in rats at doses up to 162 times the recommended human ophthalmic dose (RHOD) (*see Data*). Maternal toxicity, miscarriages and reduced fetal weights were observed in rabbits at all doses tested, with the lowest dose as 41 times the RHOD.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

An embryofetal study was conducted in pregnant rabbits administered perfluorohexyloctane by oral gavage on gestation days 6 to 19, to target the period of organogenesis.

Perfluorohexyloctane produced maternal toxicity, characterized by reduced body weight gain and food consumption, and miscarriages at all doses tested, with the lowest dose as ≥ 250 mg/kg/day (41 times the RHOD based on body surface area). Reduced fetal weights were also observed at ≥ 250 mg/kg/day but no fetal mortality or malformations. A no observed adverse effect level (NOAEL) for maternal toxicity was not established in rabbits.

An embryofetal study was conducted in pregnant rats administered perfluorohexyloctane by oral gavage on gestation days 6 to 17, to target the period of organogenesis. There was no evidence of embryofetal toxicity or teratogenicity at doses up to 2,000 mg/kg/day (162 times the RHOD).

8.2 Lactation

There are no data on the presence of perfluorohexyloctane in human milk, the effects on the breastfed infant, or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of MIEBO to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MIEBO.

8.4 Pediatric Use

The safety and effectiveness of MIEBO in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

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

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The pharmacokinetics of perfluorohexyloctane following topical ocular administration of MIEBO has not been quantitatively characterized in humans. A single pharmacokinetic (PK) study was conducted that showed low systemic perfluorohexyloctane blood levels after topical ocular administration. Perfluorohexyloctane was not metabolized by human liver microsomes in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of perfluorohexyloctane.

Perfluorohexyloctane was not mutagenic or clastogenic in a standard battery of genotoxicity tests, including a bacterial mutagenicity assay (Ames assay), an in vitro chromosome aberration assay using human peripheral lymphocytes, and an in vivo bone marrow micronucleus assay in rats.

17 PATIENT COUNSELING INFORMATION

Use with Contact Lenses

Advise patients that contact lenses should be removed prior to and for at least 30 minutes after administration of MIEBO.

Administration Instructions

Advise patients to instill one drop of MIEBO four times daily into each eye as depicted in the Administration Instructions.

Distributed by:

Bausch & Lomb Americas Inc. Bridgewater, NJ 08807 USA

Patented. See https://patents.bausch.com for US patent information.

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NEWS

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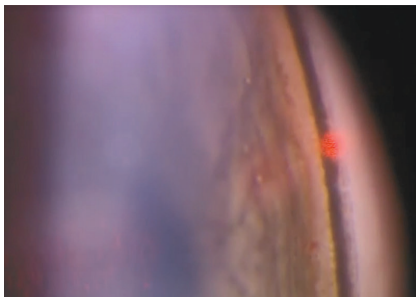
VOLUME XXXI • NO. 5

MAY 2024

SLT Before MIGS May Increase Chance of Reoperation

Given the expansion of laser trabeculoplasty and MIGS into early—sometimes initial—glaucoma management, understanding the long-term effectiveness of MIGS procedures and identifying patients most likely to benefit from them has important clinical implications. Angle-based MIGS options (canaloplasty, goniotomy, Trabectome, iStent) have grown substantially, although long-term efficacy is poorly understood. A new study based out of Massachusetts Eye and Ear in Boston analyzed angle-based MIGS effectiveness with/without preceding laser trabeculoplasty (SLT and argon laser trabeculoplasty). The team found that, while sustained IOP reduction was seen after angle-based MIGS in all groups, eyes that had laser trabeculoplasty prior were more likely to require reoperation. Their results were published in the journal *Ophthalmology Glaucoma*.

The study identified eyes that had undergone angle-based MIGS with/



without prior SLT (< two years preceding MIGS) in the IRIS Registry over a six-year period. After propensity score matching, the study identified 954 eyes undergoing standalone angle-based MIGS and 7,522 undergoing angle-based MIGS and phacoemulsification.

For eyes only undergoing angle-based MIGS, those with prior SLT were more likely to undergo reoperation vs. those without laser trabeculoplasty at six and 12 months. In multivariate models, subjects with prior SLT were more likely to undergo reoperation over the 36-month period vs. those without it (adjusted hazard ratio: 1.53). For eyes undergoing MIGS + phacoemulsification, those with prior laser trabeculoplasty were more likely to undergo reoperation vs. those without laser trabeculoplasty at 12, 24 and 36 months. The researchers also identified that baseline IOP and glaucoma secondary to medications, trauma or inflammation were associated with higher hazard ratios for reoperation.

"Our work highlights the importance of understanding populations most likely to benefit from this type of MIGS and plays a role in informing treatment decisions, managing expectations and directing future research," the researchers wrote in their paper. "While laser trabeculoplasty may provide initial IOP control, angle-based MIGS following prior laser trabeculoplasty may provide suboptimal results and the need for further surgery. Such information is useful in managing both surgeon and patient expectations."

1. Mitchell W, Yang SA, Ondeck C, et al. Effectiveness of angle based minimally invasive glaucoma surgery after laser trabeculoplasty: An analysis of the IRIS Registry. Ophthalmol Glaucoma. March 20, 2024. [Epub ahead of print].

Eye Finding Linked to Heart Attack

A recently described anatomical finding called retinal ischemic perivascular lesions (RIPLs), detected via OCT, is indicative of certain systemic cardiovascular conditions, as well as diabetes both with and without diabetic retinopathy and hypertension. More recently, they have been linked with cardiovascular conditions of coronary artery disease, atrial fibrillation and carotid artery stenosis. RIPLs are characterized by focal atrophy of the inner nuclear layer accompanied by secondary expansion of the outer nuclear layer, resulting in an undulating appearance of the middle retinal layers.

Since recent reports highlight that RIPLs can be useful in identifying subclinical cardiovascular disease, one new study wanted to determine if RIPLs are a marker of myocardial infarction (MI) in a cohort of patients with coronary artery disease (CAD). Researchers did indeed find such an association.

The retrospective investigation included 317 consecutive CAD patients who underwent spectral-domain OCT

CONTOURA® VISION

More than 20/20 vision.[1,*]
More than stunning quality.[2]
More than patient satisfaction.[2,†]

MORE THAN A NUMBER[1,2,†]

Discover patient outcomes even better **than** 20/20 with the only true topography-guided laser vision correction—CONTOURA® Vision.[1] Now with advanced **analytics** to alleviate **guesswork,** CONTOURA® Vision delivers spectacular acuity and quality[1,2,†]—making it possible to take **your patients from 20/20 to 20/More.**

CONTACT YOUR ALCON SALES REPRESENTATIVE TO LEARN MORE.

*****Clinical results from a matched group of 317 manifest eyes and 323 analytic eyes. Using the Phorcides Analytic Engine for topography-guided surgery, 41.3% of the manifest group and 62.5% of the analytic group achieved 20/16 or better UDVA.

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

References

1. Lobanoff M, Stonecipher K, Tooma T, et al. Clinical outcomes after topography-guided LASIK: comparing results based on a new topography analysis algorithm with those based on manifest refraction. *J Cataract Refract Surg*. 2020;46(6):814-819. doi:10.1097/j.jcrs.0000000000000176.

2. Stulting RD, Fant BS; T-CAT Study Group. Results of topography-guided laser in situ keratomileusis custom abalation treatment with a refractive excimer laser. *J Cataract Refract Surg*. 2016;42(1):11-18. Study description: Prospective, nonrandomized, multicenter study of 249 eyes with myopia (up to -9D) or myopic astigmatism of 6.0 D or less. Outcome measures included manifest refraction, UDVA, CDVA and visual symptoms up to 12 months.

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.

*Trademarks are the property of their respective owners.

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(SD-OCT).[1] Of all patients, 17 percent had a history of MI. A markedly higher prevalence of RIPLs was seen in the MI group at 59.3 percent compared with the non-MI group of 35.7 percent. After analysis, the researchers determined that presence of RIPLs was significantly associated with MI even after adjusting for age, sex, smoking status, hypertension, diabetes, dyslipidemia and BMI.

In their paper for the *American Journal of Ophthalmology*, the authors note that their findings are consistent with one previous study also reporting an observed higher (but not statistically significant) count of RIPLs in MI patients vs. those without. The present study confirmed these preliminary results in a larger patient base.

Another prior investigation reported RIPLs were found in 90 percent of patients with mild hypertension and only in 17 percent of healthy participants. Similarly, RIPLs have been observed in diabetic patients with and without diabetic retinopathy, with one previous report showing 94.9 percent of patients with diabetic retinopathy and 53.8 percent without exhibiting them on OCT. However, this current study found equal hypertension and diabetes prevalence among patients with and without MI, suggesting these risk factors aren't contributing to increased RIPL prevalence in the MI group.

The authors also elaborate on the association of smoking status with MI in their analysis. Only discordant results are currently available pertaining to cigarette smoking on retinal capillary plexus density. Despite this, one study has identified smoking as an independent risk factor for reduced retinal deep capillary plexus perfusion on OCT angiography.

Finally, the authors suspect that the pathophysiology of RIPLs in the setting of MI may be attributed to retinal hypoperfusion of the deep capillary plexus, either from microemboli formation or reduced ventricular ejection fraction.

Looking toward the future, the authors say, "should this association be confirmed by prospective studies, this would suggest that SD-OCT screening for RIPLs in CAD patients could be an important stratification tool for those at risk of developing MI."

They add that the findings emphasize the critical role of RIPL detection in patients with coronary artery disease.

1. Bousquet E, Santina A, Au A, et al. Retinal ischemic perivascular lesions are associated with myocardial infarction in patients with coronary artery disease. Am J Ophthalmol. March 27, 2024. [Epub ahead of print].

Consultations for Papilledema on the Rise

Once a relatively rare basis for consultation with a hospital emergency department or specialty practice, concern over suspected papilledema has grown in recent years. Many different factors are responsible for this ongoing change, including greater incidence of idiopathic intracranial hypertension (IIH), overreported radiologic signs of intracranial hypertension, strained access to outpatient neuro-ophthalmology services, poor insurance coverage and medicolegal concerns. These are all contributors to the lower threshold for emergency department visits for papilledema.

Consequently, one group of researchers wanted to examine the referral patterns and outcomes of neuro-ophthalmology ED and inpatient consultations for cases of concern for papilledema. Over one year, 153 consecutive patients were referred for concern of papilledema to a university-based subspecialty care center (Emory University) and underwent the institution's standardized "papilledema protocol."[1]

After completing the protocol, it was determined that 58 percent of cases had bilateral optic disc edema, with 89 percent of those showing signs of papilledema (IIH). Of the 25 percent of the total consultations for suspected intracranial pressure without previous fundus exam, 74 percent did not have optic disc edema, 21 percent had papilledema and 5 percent had other causes of bilateral disc edema.

Of the 58 percent of consultations for presumed papilledema seen on fundus examination, 58 percent had confirmed papilledema, 17 percent had pseudopapilledema and 9 percent had other causes of bilateral optic disc edema. Of the 17 percent of patients with known IIH, five had papilledema and four required urgent intervention. Most diagnosed was IIH. Patients with secondary causes of IIH were on average older, men, not obese and more likely to have neurologic symptoms compared with IIH.

In total, the most common cause of bilateral disc edema was nonfulminant IIH in 64 percent of all referred patients without a previous diagnosis. The other 36 percent were diagnosed with a vision- or life-threatening disease, with 18 patients having papilledema from severe neurologic disorders.

The study authors note that "it is impossible to predict which papilledema patients will have a potentially severe cause of raised intracranial pressure without urgent brain imaging, and even in cases of newly diagnosed IIH, predicting which patients will have a poor visual outcome and require urgent multidisciplinary treatment is challenging, highlighting the need for urgent evaluation."

Seven urgent surgical interventions were performed in this IIH cohort to prevent vision loss, including two optic nerve sheath fenestrations, two primary cerebrospinal fluid shunting procedures and three shunt revisions.

The authors continue, pointing out that "given the limited access to neuro-ophthalmologists, our study supports the need for ED access to

(Continued on p. 16)

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REFERENCES:
1. REF2022CT4107 Z311524E_A TECNIS Eyhance™ IOL with TECNIS SIMPLICITY™ Delivery System US DFU.
2. REF2021CT4007 Z311525E_A TECNIS Eyhance™ Toric II IOL with TECNIS SIMPLICITY™ Delivery System DFU.
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WARNINGS: Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the Directions for Use that could increase complications or impact patient outcomes. The lens should be placed entirely in the capsular bag. Do not place the lens in the ciliary sulcus. Rotation of the TECNIS Eyhance™ Toric II IOL from its intended axis can reduce its astigmatic correction. Misalignment greater than 30° may increase postoperative refractive cylinder. If necessary, lens repositioning should occur as early as possible, prior to lens encapsulation. Do not attempt to disassemble, modify or alter the delivery system or any of its components, as this can significantly affect the function and/or structural integrity of the design. Do not implant the lens if the rod tip does not advance the lens or if it is jammed in the delivery system. The lens and delivery system should be discarded if the lens has been folded within the cartridge for more than 10 minutes.

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ADVERSE EVENTS: The most frequently reported cumulative adverse event that occurred during the SENSAR® 1-Piece IOL clinical trial was cystoid macular edema which occurred at a rate of 3.3%.

ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

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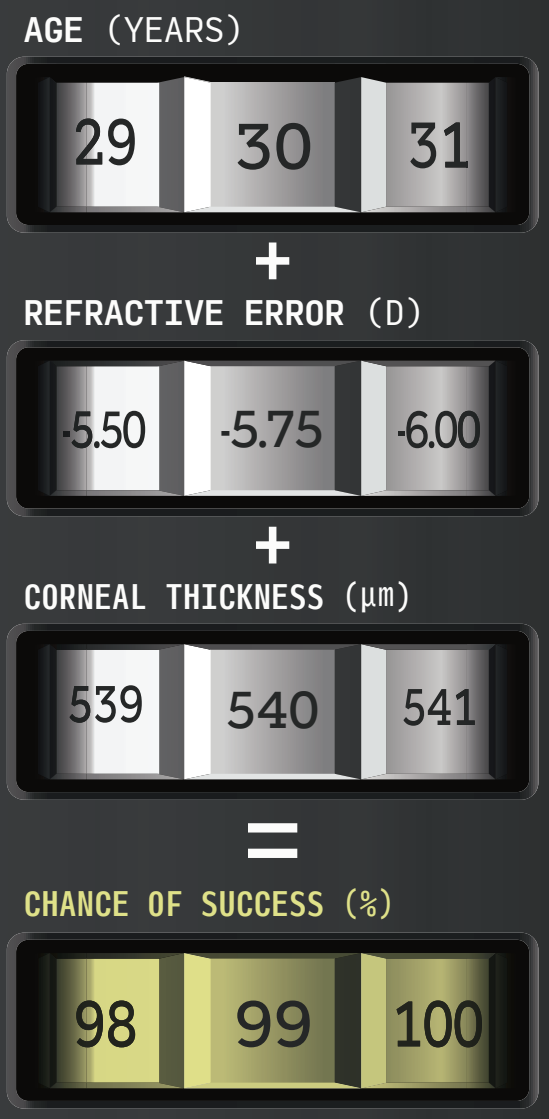

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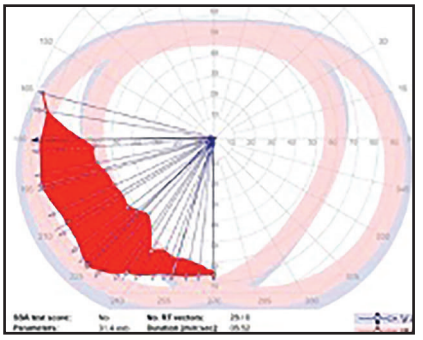

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30

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INDICATION

RYZUMVI™ (phentolamine ophthalmic solution) 0.75% is indicated for the treatment of pharmacologically-induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Uveitis:** RYZUMVI is not recommended to be used in patients with active ocular inflammation (e.g., iritis).
- **Potential for Eye Injury or Contamination:** To avoid the potential for eye injury or contamination, care should be taken to avoid touching the vial tip to the eye or to any other surface.
- **Use with Contact Lenses:** Contact lens wearers should be advised to remove their lenses prior to the instillation of RYZUMVI and wait 10 minutes after dosing before reinserting their contact lenses.

Adverse Reactions

The most common adverse reactions that have been reported are instillation site discomfort (16%), conjunctival hyperemia (12%), and dysgeusia (6%).

Please see Brief Summary of Prescribing Information on the adjacent page and the full Prescribing Information at RYZUMVI.com.

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BRIEF SUMMARY: Consult the full Prescribing Information for complete product information available at www.RYZUMVI.com

INDICATIONS AND USAGE: RYZUMVI is indicated for the treatment of pharmacologically-induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS
- **Uveitis:** RYZUMVI is not recommended when active ocular inflammation (e.g., iritis) is present because adhesions (synechiae) may form between the iris and the lens.
- **Potential for Eye Injury or Contamination:** To avoid the potential for eye injury or contamination, care should be taken to avoid touching the vial tip to the eye or to any other surface.
- **Use with Contact Lenses:** Contact lens wearers should be advised to remove their lenses prior to the instillation of RYZUMVI and wait 10 minutes after dosing before reinserting their contact lenses.

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

RYZUMVI was evaluated in 642 subjects in clinical trials across various subject populations. The most common ocular adverse reactions reported in >5% of subjects were instillation site discomfort including pain, stinging, and burning (16%) and conjunctival hyperemia (12%). The only non-ocular adverse reaction reported in >5% of subjects was dysgeusia (6%).

USE IN SPECIFIC POPULATIONS
Pregnancy: Risk Summary: There are no available data with RYZUMVI administration in pregnant women to inform a drug-associated risk. In animal toxicology studies, when phentolamine was administered orally to pregnant mice and rats during the period of organogenesis skeletal immaturity and decreased growth was observed in the offspring at doses at least 24-times the recommended clinical dose. Additionally, a lower rate of implantation was seen in pregnant rats treated with phentolamine administered at least 60-times the recommended clinical dose. No malformations or embryofetal deaths were observed in the offspring of pregnant mice, rats, and rabbits administered phentolamine during the period of organogenesis at doses of at least 24-, 60-, and 20-times, respectively, the recommended clinical dose (see Data). RYZUMVI should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Data *Animal Data* Oral administration of phentolamine to pregnant rats and mice at doses at least 24-times the recommended clinical dose (based on a body weight per surface area (mg/m^2) comparison with a 60-kg human) resulted in slightly decreased growth and slight skeletal immaturity of the fetuses. Immaturity was manifested by increased incidence of incomplete or unossified calcanei and phalangeal nuclei of the hind limb and of incompletely ossified sternebrae. At oral phentolamine doses at least 60-times the recommended clinical dose (based on a mg/m^2 comparison with a 60-kg human), a slightly lower rate of implantation was found in rats. Phentolamine did not affect embryonic or fetal development in rabbits at oral doses at least 20-times the recommended dose (based on a mg/m^2 comparison with a 60-kg human). No malformations or embryofetal deaths were observed in the rat, mouse or rabbit studies.
Lactation: Risk Summary: There is no information regarding the presence of phentolamine in human milk, the effects on the breastfed infants, or the effects on milk production during lactation to inform risk of phentolamine ophthalmic solution 0.75% to an infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RYZUMVI and any potential adverse effects on the breastfed child from RYZUMVI.
Pediatric Use: The safety and effectiveness of RYZUMVI have been established in pediatric patients aged 3 to 17 years. No overall differences have been observed between pediatric and adult subjects.
Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger adult subjects.

OVERDOSAGE
No deaths due to acute poisoning with phentolamine have been reported. Overdosage with parenterally administered phentolamine is characterized chiefly by cardiovascular disturbances, such as arrhythmias, tachycardia, hypotension, and possibly shock. In addition, the following might occur: excitation, headache, sweating, visual disturbances, nausea, vomiting, diarrhea, or hypoglycemia. There is no specific antidote; treatment consists of appropriate monitoring and supportive care. Substantial decreases in blood pressure or other evidence of shock-like conditions should be treated vigorously and promptly.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Carcinogenesis: Carcinogenicity studies with RYZUMVI have not been conducted.
Mutagenesis: Phentolamine was not mutagenic in the in-vitro bacterial reverse mutation (Ames) assay. In the in-vitro chromosomal aberration study in Chinese hamster ovary cells, numerical aberrations were slightly increased after a 4-hour exposure to phentolamine without metabolic activation, and structural aberrations were slightly increased after a 4-hour exposure to phentolamine with metabolic activation only at the highest concentrations tested, but neither numerical nor structural aberrations were increased after a 20-hour exposure without metabolic activation. Phentolamine was not clastogenic in two in-vivo mouse micronucleus assays.
Impairment of Fertility: The effect of phentolamine on female fertility has not been studied. Male rats treated with oral phentolamine for nine weeks (four weeks prior to mating, 3 weeks during the mating period and 2 weeks after mating) were mated with untreated females. At doses up to 648-times human therapeutic exposure levels at the C_{max}, no adverse effects on male fertility parameters or on reproductive parameters in the untreated females mated with the treated males were observed.

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REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

The Devil's in The Details

It's funny how, in the span of maybe two or three years, artificial intelligence exploded and is suddenly everywhere. In the beginning, studies of AI's abilities were singular and appeared in journals at a gradual pace. Now, however, reports of AI's latest triumphs are coming so fast, you need an AI to keep up with them.

A study from the University of Cambridge in the U.K. gave mock ophthalmology exam questions to several AI systems, expert ophthalmologists and trainees. The answers were graded by a masked panel of ophthalmologists. They found that the AI GPT-4 outperformed the trainees, and even compared favorably to the expert ophthalmologists.[1]

Another study from Mt. Sinai in New York City tested an AI and fellowship-trained ophthalmologists on a set of ophthalmological questions and patient cases from the realms of glaucoma and retina. The researchers found that ophthalmologists rated the machine's accuracy and completeness higher than the physicians'.[2]

In medicine in general, Google's medical-oriented AI, Med-PaLM 2, recently became the first artificial intelligence to rank as an "expert" in performance on a MedQA dataset of U.S. Medical Licensing Exam-style questions.[3] It achieved an accuracy of more than 85 percent. It also was the first AI to score a 72.3 percent on Indian AIIMS and NEET medical examination questions.[3]

So, AI is everywhere, including in the popular document creation/editing software Adobe Acrobat in the form of an "AI Assistant." Since Acrobat is one of the programs we use extensively here at *Review*, the staff naturally wanted to test the AI Assistant to see what it could do.

One of the Assistant's functions is it allows you to "feed" it a journal article and it'll summarize it for you, as well as answer queries about it. Perfect! Who wouldn't want a quicker way to digest all the data we're bombarded with daily?

So, with visions of the Supreme Intelligence that's beating physicians all over the place, our editors fed some articles to the AI Assistant—and got a reality check.

Though some results were useful, it also did things like refer to a treatment in the "subconscious intellispace," rather than the subconjunctival space. The errors it makes are subtle, as one editor put it, so you have to go through them line by line to check for accuracy. (You might as well just summarize the article yourself at that point.) "Sometimes the AI extrapolates too much from a single sentence it's identified as being important," she said. "It writes very well, so it's easy to read its output and believe it's true."

Let these words ring in your ears the next time you're analyzing the output of a chatbot, Large Language Model or other AI system. As the saying goes: "Trust—but verify."

— Walter Bethke
Editor in Chief

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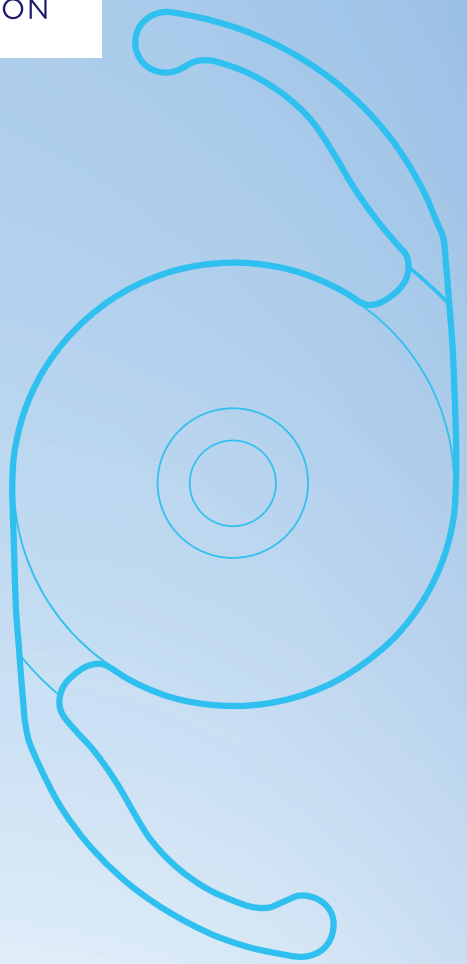

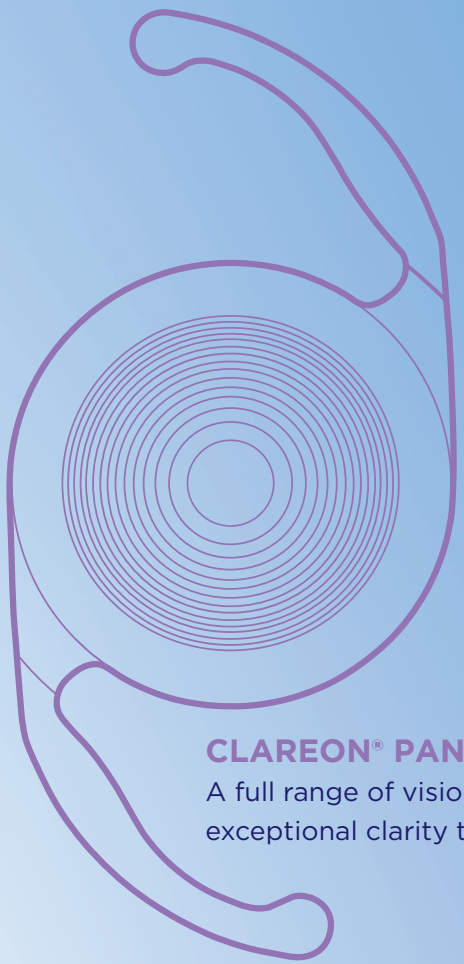

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* Defined as modified Miyata grade 0, <25mv/mm^2 over 3 years (n=138), and over 9 years (n=20), respectively. PCIOL=Presbyopia Correcting IOL.
† Results from a prospective, randomized, parallel group, subject- and assessor-masked, multisite trial of 107 subjects bilaterally implanted with the AcrySof® IQ Vivity® Extended Vision IOL and 113 with the AcrySof® IQ IOL with 6 months follow-up.
‡ Snellen VA was converted from logMAR VA. A Snellen notation of 20/20-2 or better indicates a logMAR VA of 0.04 or better, which means 3 or more of the 5 ETDRS chart letters in the line were identified correctly.

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Alcon

(Continued from p. 7)

expert eye-care providers or ocular fundus camera with remote interpretation of images for prompt identification of optic disc edema and standardized evaluation for neurologic emergencies such as with a 'papilledema protocol.'"

Finally, they speculate that, in the future, implementation of nonmydriatic ocular fundus cameras and potential use of AI-assisted triage may allow for expedited workup in unspecialized health-care facilities.

1. Ray HJ, Smolar ALO, Dattilo M, et al. The increasing burden of emergency department and inpatient consultations for 'papilledema'. J Neuroophthalmol. March 19, 2024. [Epub ahead of print].

Childhood Obesity and IOP

In a recent study published in *Journal of Glaucoma*, a team in Turkey investigated the effect of obesity on corneal biomechanics as measured by Ocular Response Analyzer (Reichert), retinal nerve fiber layer and central macular thickness in children.[1]

This prospective, cross-sectional, comparative study evaluated 146 eyes of normal-weight, overweight and obese children between the ages of six and 17 (43 boys and 30 girls). Mean age among the three groups was 12.5, 13.2 and 13.5, respectively. BMI percentile was found to be 44.5 percent, 88.8 percent and 98.7 percent, respectively.

They found that the mean IOP value was significantly higher in obese but not in overweight children; however, the mean hysteresis and corneal resistance factor values are significantly higher not only in obese but also overweight children. There was no statistically significant difference regarding age, sex, corneal compensated IOP, average RNFL thickness, cup-to-disc ratio or central macular thickness among the groups.

The researchers suggest the possibility that "excess weight may alter the composition or structure of the cornea, leading to changes in its biomechanical properties."

The team did note that the biometric characteristics of the study eyes, such as central corneal thickness and axial length measurements, weren't taken into account, which may have influenced the study outcomes.

The researchers believed that their study underscores the importance of regular IOP and retinal assessments for early detection and management. "The significant elevation in corneal hysteresis and corneal resistance factor values observed in overweight children compared with those of normal weight implies that corneal biomechanics may be one of the parameters to be considered in the diagnosis and follow-up of these children," they concluded. ◀

1. Eroglu SA, Unsal AIA, Verdi F, et al. The effect of childhood obesity on intraocular pressure, corneal biomechanics, retinal nerve fiber layer and central macular thickness. J Glaucoma. March 19, 2024. [Epub ahead of print].

On a Knife's Edge

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER, MD
CHIEF MEDICAL EDITOR

Lest you worry that I take everything too seriously, I do enjoy the occasional TV show. Can we still call them "TV shows" if the TV is nothing more than a monitor for other media? Showing my age again. And one of the few shows I can tolerate is "The Big Bang Theory," and its prequel "Young Sheldon," the story of an annoying, but inadvertently funny, boy genius. It's funny in part because he grows up in a religious family while trying to live the scientific life. Sheldon doesn't believe in God, much to the distress of his mother.

In a recent episode, his mother is distraught about her pending divorce and has given up on the concept of God. Sheldon, trying to console her, points out that the scientific underpinning of our universe is so fantastically precise that it couldn't be an accident, that there had to be a guiding force or we wouldn't exist at all. He was referencing the 'fine-tuned universe' concept. If you're not familiar with this, sit down. It's pretty mind-blowing.

The physical universe is based on a number of scientific constants: Charge on an electron, force of gravity, etc. If any, and I mean any, of these were to be even the smallest amount different our universe would not exist. Or as Stephen Hawking put it: "The universe and the laws of physics seem to have been specifically designed for us. If any one of about 40 physical qualities had more than slightly different values, life as we know it could not exist: Either atoms would not be stable, or they wouldn't combine into molecules, or the stars wouldn't form heavier elements, or the universe would collapse before life could develop, and so on ..." And since humans are so anthropomorphic, much writing on this subject focuses on the chances of life not existing. But really it's much bigger than that: Reality wouldn't exist. There would be no physical universe. For me that concept is far more disturbing than whether there would be humans running around. There's room in this theory for an almost optimized set of variables where life is more than possible, it's probable. But that's threading the needle given it's more likely than not nothing is possible.

So how did this happen? Is there a deity who saw to it that everything was perfectly adjusted so that reality happened and life happened? How could something like this, so insanely precisely necessary occur on its own? Were or are there other realities where some of the parameters were "close but no cigar"? Hence, the theory of the multiverse: Imperfectly formed realities other than our own. It's pretty presumptuous to believe ours is perfect. It's perfect for us, but that's all we can say.

I'm pretty much an atheist, maybe agnostic at times, having become too disillusioned to think there's an overarching benevolent force out there. However, it's tough to imagine that a set of physical properties just spontaneously appeared, all exactly perfect for a stable and life-friendly reality to come into existence.

Talk about long odds.

We exist on a knife's edge of the possible. Through the grace of God or chance, forces so minute must be what they must be. It's in conflict with how most of us live our lives. We allow for tolerances, for variability, for wiggle room. Turns out in the very big and very small pictures there isn't any. To go back to Stephen Hawking, "So long as the universe had a beginning, we could suppose it had a creator. But if the universe is really self-contained, having no boundary or edge, it would have neither beginning nor end, it would simply be. What place, then, for a creator?" No matter how you approach this, it's a wonder to contemplate that we were so fortunate. Just wish I knew who to thank .... ◀

This article has no commercial sponsorship. **Dr. Blecher** is an attending surgeon at Wills Eye Hospital.

Strategies for Chemical Injury

Early management is key for a successful outcome. Here's how to approach these eyes.

LAURA PALAZZOLO, MD
NEW YORK

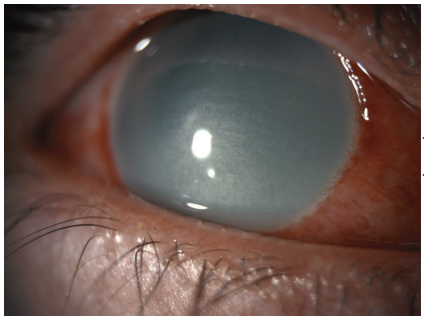
Chemical injuries to the eye can have serious consequences and require prompt and appropriate management. Individuals who work around chemicals are most at risk for this type of injury, and we encourage this population to wear eye protection every time they're handling chemicals. That said, many of the chemical injuries we see occur in individuals doing cleaning or house projects who aren't well-versed in eye safety and protection. As we move towards "spring cleaning" these injuries become even more common. I had a patient who was opening his pool without eye protection and chlorine splashed back into his eyes, causing very severe injury.

Here, I'll discuss the steps necessary when dealing with ocular chemical injury, from substance identification and classification to medical and surgical management.

Initial Steps

Limiting the amount of contact the chemical substance has with the eye is crucial. Most ocular chemical injury patients come through the emergency department, which is where we're best able to irrigate the eye with something like a Morgan lens. However, because time to irrigation greatly influences visual prognosis, it's recommended that patients who can't get to the emergency department right away irrigate with whatever they have on hand, even if it's not sterile, such as tap water.

When performing the initial exam, ensure that all of the toxic substance is fully out of the eye. Carefully flip the eyelids and evaluate underneath with a cotton tip, checking for any remaining fragments or debris that could cause persistent damage. I've had one case of wet concrete exposure where concrete bits stuck deep in the fornix and continued to leak chemicals and cause injury. This wasn't initially identified in the emergency department, and pH remained high despite continuous irrigation.



Laura Palazzolo, MD, and Alex Mammen, MD

Figure 1. An alkali burn (sodium hydroxide degreasing solution: pH 13-14) 10 days after accident with complete stromal opacification of the cornea, 100-percent corneal epithelial defect and 360-degree-conjunctival epithelial defect.

Acidic vs. Alkali Burns

Understanding the nature of the

Table 1. Dua Classification for Ocular Chemical Injury

Grade	Prognosis	Clinical Findings	Conjunctival Involvement	Analogue Scale
I	Very good	0 clock hours of limbal involvement	0 percent	0/0 percent
II	Good	≤3 clock hours of limbal involvment	≤30 percent	0.1 to 3/1 to 29.9 percent
III	Good	3 to 6 clock hours of limbal involvement	30 to 50 percent	3.1 to 6/31 to 50 percent
IV	Good to guarded	6 to 9 clock hours of limbal involvement	50 to 75 percent	6.1 to 9/51 to 75 percent
V	Guarded to poor	9 to <12 clock hours of limbal involvement	75 to <100 percent	9.1 to 11.9/75.1 to 99.9 percent
VI	Very poor	Total (12 clock hours) limbal involvement	100 percent	12/100 percent

This article has no commercial sponsorship.

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chemical substance and its mechanism of injury at each phase is important for management. Acidic and alkali damage have several important differences:

• Acidic substances create a fair level of damage, but this damage is usually limited to the surface, to the epithelium and the skin. With the exception of hydrofluoric acid, acids denature and precipitate the tissue proteins they come into contact with, so they create their own coagulated protein barrier that blocks further penetration into the eye.

• Alkali substances are lipophilic and saponify fatty acids of cell membranes, allowing them to rapidly penetrate the corneal stroma and enter into the anterior chamber, causing many levels of damage (*Figure 1*). Mucous membrane loss, meibomian gland dysfunction with long-term dry-eye complications, limbal stem cell deficiency and even glaucoma are all possible consequences of intraocular penetration.

Be sure to confirm the pH level of the substance and check the eye's pH level until it neutralizes to 7.

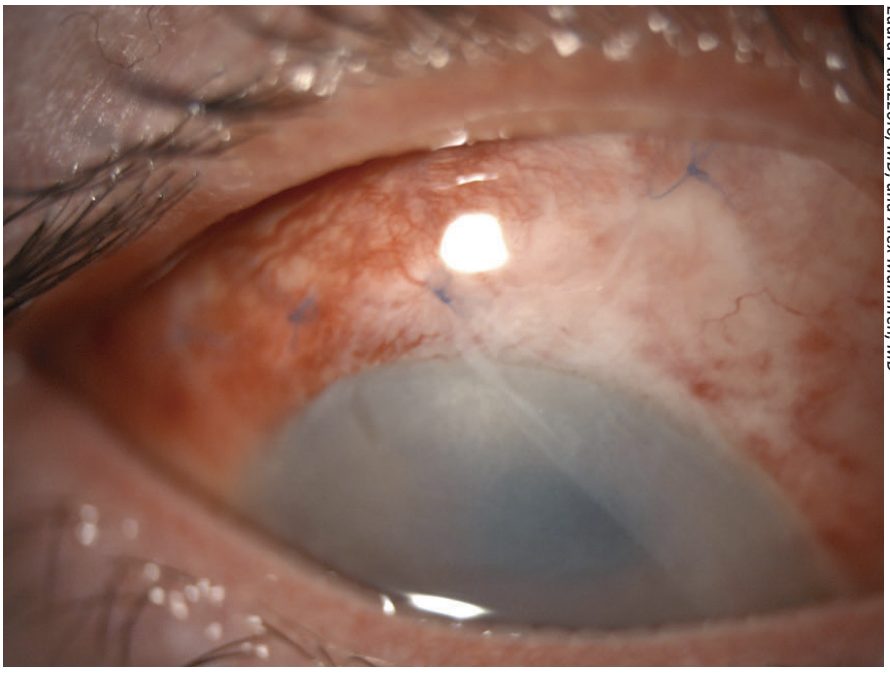
Classification

There are two main classification systems for the prognosis of ocular chemical injury. The Dua classification system considers the estimated degree of limbal and bulbar conjunctival involvement, with an analogue scale representing the amount of limbal involvement in clock hours divided by the percentage of conjunctival involvement (*Table 1*).

The Roper Hall classification system characterizes the corneal injury based on corneal involvement (e.g., epithelial damage, corneal haze, corneal opacification) and the amount of limbal ischemia (*Table 2, page 69*). Both systems are used in clinical practice, with varying evidence in the literature for their prognostic values.

Medical Management

Conventional medical management for chemical injury focuses on controlling inflammation in the eye and creating an optimal healing environment.



Laura Palazzolo, MD, and Alex Mammen, MD

Figure 2. Sutured amniotic membrane.

The body and eye respond to chemical injury by producing inflammatory factors, and this inflammatory response can precipitate further damage even beyond what the chemical itself did. Early on, medical treatment should focus on limiting inflammation by promptly administering a topical corticosteroid such as prednisolone acetate. For severe chemical injuries with limbal involvement and corneal opacification, start with a high-frequency dose, about every one to two hours. For milder injuries, administer corticosteroids four times daily. Steroid dosages must be decreased and tapered within the first week or two to allow the eye to heal.

For cases with epithelial defect or any range of injury, antibiotics are given to prevent infection. A cycloplegic such as atropine or cyclopentolate can be given for comfort.

There's evidence for using 1% medroxyprogesterone as an alternative to a corticosteroid or after corticosteroid treatment. This progestational steroid also limits inflammation, but as a collagenase inhibitor, it allows for stromal repair to take place. Oral doxycycline, another collagenase inhibitor, and vitamin C, which promotes collagen synthesis, also foster healing. Oral vitamin C is commonly used, but there's also evidence for using 10% ascorbic acid drops applied hourly.

To promote healing, it's important to keep the eye well-lubricated. Preservative-free artificial tears can be given hourly. Autologous serum tears or platelet-rich plasma are options with similar efficacy for severe dryness.

When assessing dryness, pay special attention to the eyelids and how they sit. Chemical injury management often warrants an interdisciplinary approach with oculoplastics to address other issues that contribute to dryness such as scarring, symblephara and lagophthalmos. A temporary tarsorrhaphy early on can help with healing if the eyelids aren't apposing well.

If necrosis occurs early on, debride the epithelium and place an amniotic membrane to aid corneal healing. Amniotic membrane transplantation (*Figure 2*) or mucous membrane grafting is also used in cases requiring fornix reconstruction or with significant conjunctival involvement. Timing is important when using amniotic membrane for chemical injuries. It's

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*The exact mechanism of action is unknown.
†Tyrvaya was evaluated across 3 randomized, vehicle-controlled, double-masked studies in which adults aged ≥22 years diagnosed with dry eye disease received 1 spray of either active drug or vehicle in each nostril twice daily. Primary endpoint: % of patients with mean change from baseline in STS of ≥10 mm at week 4 in ONSET-1: 52% with Tyrvaya (n=48) vs 14% with vehicle (n=43) and in ONSET-2: 47% with Tyrvaya (n=260) vs 28% with vehicle (n=252). Onset of action: mean change from baseline in STS ~5 minutes after first dose (not a prespecified endpoint) in ONSET-1 was 17.2 mm with Tyrvaya (n=48) vs 4.0 mm with vehicle (n=43) and in ONSET-2 was 16.5 mm with Tyrvaya (n=260) vs 6.9 mm with vehicle (n=251). Observed data. On Day 1 in clinical studies, a baseline anesthetized Schirmer's test was performed. Tyrvaya was then administered concurrently with Schirmer's test. Schirmer's test results were measured at ~5 minutes. Mean change from baseline in STS at week 12 in the MYSTIC study was 10.8 mm with Tyrvaya vs 6.0 mm with vehicle. Limitations: Ex-US, single-center study. All subjects were Hispanic or Latino. Tyrvaya group mean baseline STS 5.5 mm (n=41); vehicle group mean baseline STS 5.3 mm (n=41). All randomized and treated patients were included in the analysis and missing data were imputed using last-available data. [2-8]
See references on next page.

Indication
Tyrvaya® (varenicline solution) nasal spray is indicated for the treatment of the signs and symptoms of dry eye disease.

Important Safety Information
The most common adverse reaction reported in 82% of patients was sneezing. Events that were reported in 5-16% of patients were cough, throat irritation, and instillation-site (nose) irritation.

Please see Brief Summary of Prescribing Information on the next page and the full Prescribing Information at Tyrvaya-pro.com.

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INDICATIONS AND USAGE

TYRVAYA® (varenicline solution) nasal spray is a cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease.

ADVERSE REACTIONS

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

In three clinical trials of dry eye disease conducted with varenicline solution nasal spray, 349 patients received at least 1 dose of TYRVAYA. The majority of patients had 31 days of treatment exposure, with a maximum exposure of 105 days.

The most common adverse reactions reported in 82% of TYRVAYA treated patients was sneezing. Other common adverse reactions that were reported in >5% of patients include cough (16%), throat irritation (13%), and instillation-site (nose) irritation (8%).

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: There are no available data on TYRVAYA use in pregnant women to inform any drug associated risks. In animal reproduction studies, varenicline did not produce malformations at clinically relevant doses.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US 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.

Data: *Animal Data*: Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (4864 times the MRHD on a mg/m^2 basis).

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day (1216 times the MRHD on a mg/m^2 basis). Decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

Lactation: Risk summary: There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

The lack of clinical data during lactation precludes a clear determination of the risk of TYRVAYA to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TYRVAYA and any potential adverse effects on the breastfed child from TYRVAYA.

Pediatric Use: Safety and efficacy of TYRVAYA in pediatric patients have not been established.

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

References: 1. Jones L, Downie LE, Korb D, et al. *Ocul Surf.* 2017;15(3):575-628. **2.** Tyrvaya. Prescribing Information. Oyster Point Pharma; 2021. **3.** Oyster Point Pharma. Data on file. OPP-002 (ONSET-1) Clinical Study Report. August 4, 2019. **4.** Oyster Point Pharma. Data on file. OPP-101 (ONSET-2) Interim Clinical Study Report. October 13, 2020. **5.** Quiroz-Mercado H, Hernandez-Quintela E, Chiu KH, Henry E, Nau JA. *Ocul Surf.* 2022;24:15-21. **6.** Wirta D, Torkildsen GL, Boehmer B, et al. *Cornea.* 2022;4(10):1207-1216. **7.** Wirta D, Vollmer P, Paauw J, et al. *Ophthalmology.* 2021;0(0):379-387. **8.** Oyster Point Pharma. Data on file. OPP-004 (MYSTIC) Clinical Study Report. March 19, 2020.

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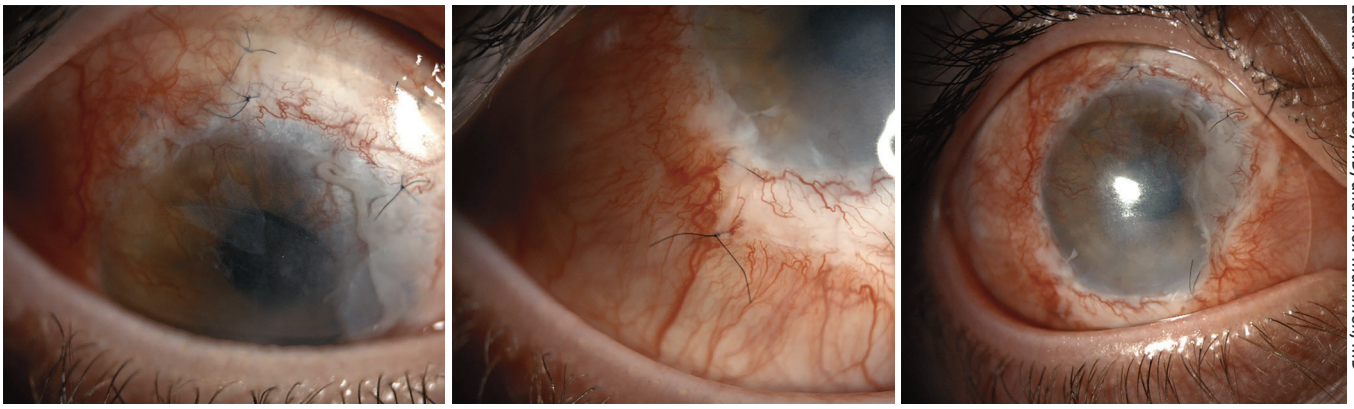

Laura Palazzolo, MD, and Alex Mammen, MD

Figure 3. One week after conjunctival limbal autograft.

most effective when applied within the first two weeks.

Surgical Management

When it comes to surgical intervention, set yourself and the patient up for success and wait for the right conditions. I always counsel patients with severe chemical injury that the road to healing is a slow one. There are several steps, and much of it consists of waiting and continuing the same treatment until the eye is at a point where it's ready for surgery.

At the two- to three-week point, begin assessing the level of limbal stem cell involvement and damage. However, before undertaking any surgical treatments, ensure the eye has healed and the ocular surface and tear film have improved. If oculoplastics needs to intervene with the eyelids, this should absolutely be done before turning to the limbal stem cells. While a limbal stem cell transplant could be done as early as two weeks, it's generally best to wait and perform the procedure on a non-inflamed eye.

There are three primary types of limbal stem cell transplantation:

• ***Conjunctival limbal autograft.*** If the patient's chemical injury is unilateral and the fellow eye is healthy, consider an autograft procedure (*Figures 3 and 4*). Before doing a transplant, be sure to remove any scarring or pannus.

From the fellow eye, excise 4 to 6 clock hours of limbal tissue and a small amount of adjacent conjunctiva. Avoid taking too much tissue from the healthy eye, as this carries the risk of that eye developing limbal stem cell deficiency. Divide the limbal tissue into two segments and place them on the recipient eye about 12 clock hours apart. This tissue will integrate into the recipient eye to aid corneal re-epithelialization and reduce any conjunctivalization that's occurred with the limbal stem cell deficiency. (View a video of a CLAU procedure in the online version of this article at reviewofophthalmology.com.)

• ***Conjunctival limbal allograft.*** If the patient has a bilateral injury, an allograft procedure may be needed. Limbal stem cell donor tissue can come from a living relative or a deceased donor in the form of a cadaveric transplant. This approach is effective, but it's accompanied by the risk of graft rejection and the need for the pa-

(Continued on p. 69)

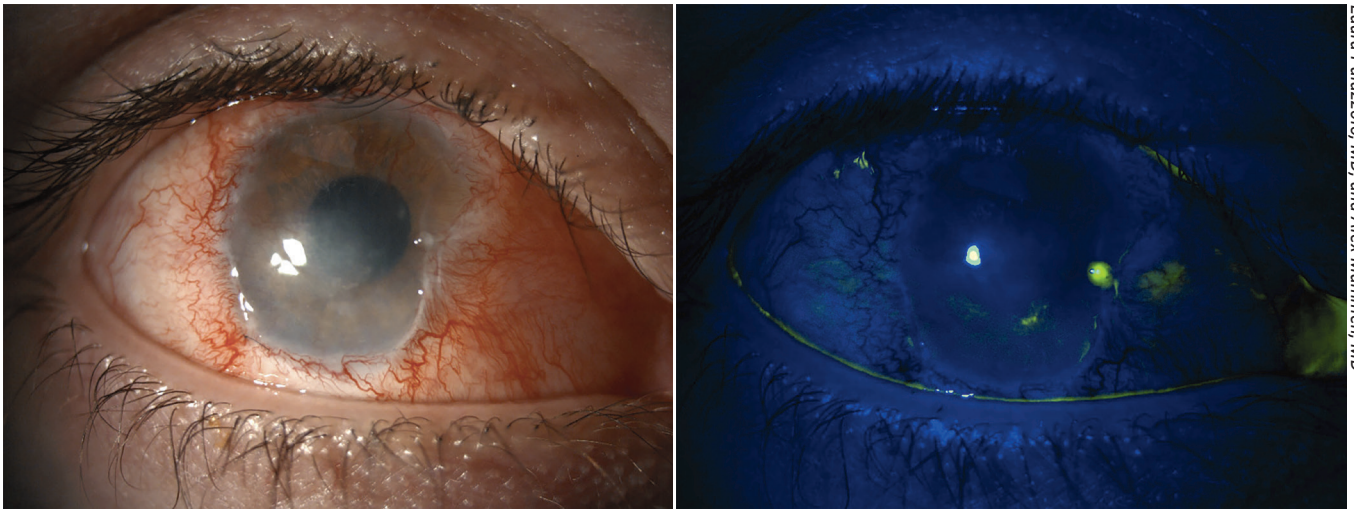

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Figure 4. One month after conjunctival limbal autograft with reduced vascularization at graft sites and healed epithelium.

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SCAN FOR MORE INFO

Managing the Mystery of Dysphotopsias

Although these unwanted phenomena continue to occur, there are ways to help patients overcome the symptoms.

LIZ HUNTER
SENIOR EDITOR

In all his years as a cataract and refractive surgeon, Samuel Masket, MD, of Advanced Vision Care, and clinical professor at the Stein Eye Institute, UCLA, is still perplexed by dysphotopsias. "They're fascinating and there's no simple theory to explain them," he says. "That's why I continue to study them. I like to solve the unsolvable."

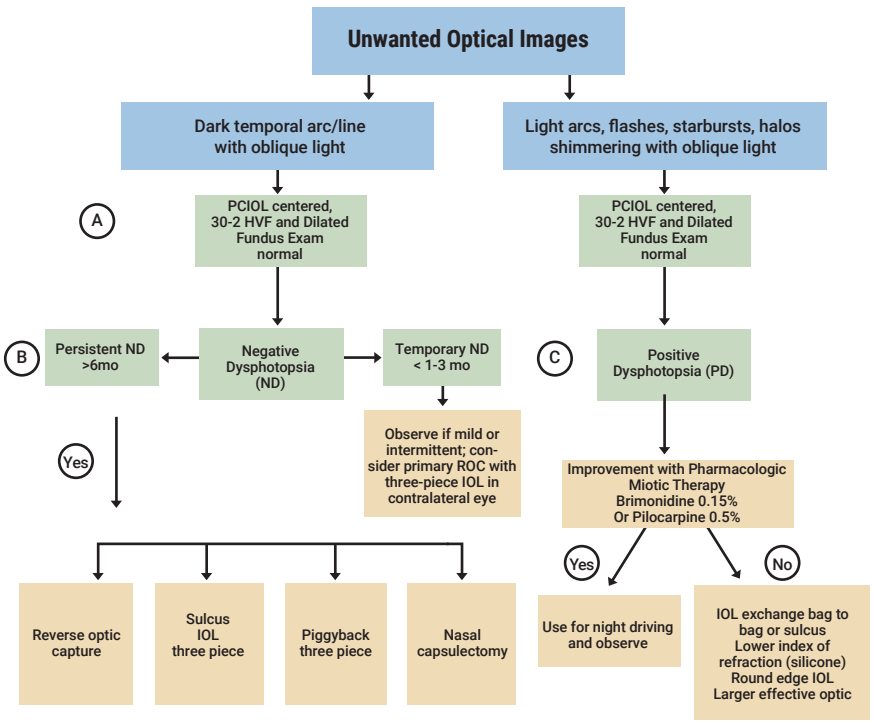
Puzzling as they may be, good research exists that dysphotopsias can be managed by surgeons who take time to address their patients' concerns. We spoke with several physicians who offered their experiences in mitigating these disturbances.

Describing Dysphotopsias

Dysphotopsias have become a recognized phenomenon that occurs following an otherwise uncomplicated cataract surgery and implantation of monofocal IOLs. "They're a common cause of patient dissatisfaction," says Linda Tsai, MD, FACS, a professor in the department of ophthalmology and visual sciences at Washington University in St. Louis. "It can be very frustrating and anxiety-provoking for the patients when, after surgery, they notice new visual disturbances. These dysphotopsias have two types. Positive dysphotopsias are usually bright, flickering lights off to the side of their vision. Sometimes if they put their hand up, it doesn't seem to be there as much. Patients can describe this as 'something always flashing on the side part of my vision.'"

The second type is negative dysphotopsias. "These are very commonly described as a dark, crescent-shaped shadow on the temporal side of their vision," Dr. Tsai continues. "These can be very bothersome and disturbing to patients. Positive dysphotopsias have been reported in over 60 percent of patients in a previous study, but they often go away and are less likely to necessitate a surgical intervention. Negative dysphotopsias are reported to be less common (less than 30 percent), but these are more commonly the ones that might need surgical intervention later on if patients don't neuroadapt."

Positive dysphotopsias were first described in 1993 by Dr. Masket and co-authors.[1] Their research determined that the undesired optical images were produced by the shape of the ovoid IOLs used at that time. Negative dysphotopsias were de-

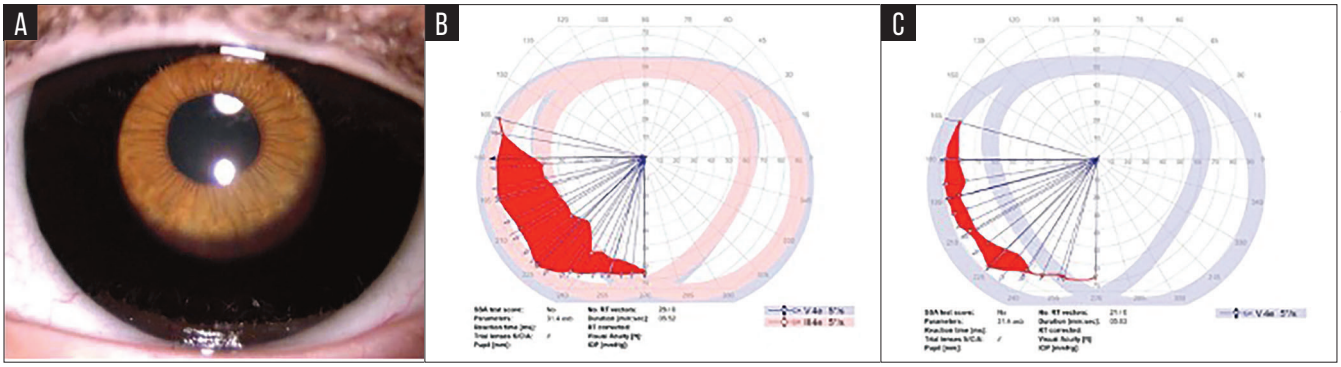


Samuel Masket, MD

Dysphotopsias often resolve on their own over time, but some conservative management strategies can help patients find relief initially. If the symptoms persist, surgeons can turn to surgical interventions as a last resort.

This article has no commercial sponsorship.

Dr. Chayet is considered a pioneer in refractive and cataract surgery, and is the medical director of the Codet Vision Institute in Tijuana, Mexico. He is a clinical investigator for RxSight, LensGen and ForSight Vision6.



Samuel Masket, MD

When Samuel Masket, MD, and colleagues conducted visual field testing on patients with negative dysphotopsias, they found the scotoma to be far greater in extent when both eyes were fully open (B) than when a peripherally occluding contact lens (A) was applied to the fellow eye (C).[7] This suggests the involvement of the central nervous system, according to Dr. Masket.

scribed in 2000 by James A. Davidson, MD.[2] These have been linked to the squared edge of IOLs, which were popularized for their reduced risk of posterior capsule opacification. More recently, ray-tracing optical modeling described the cause of negative dysphotopsias as an "illumination gap" between rays refracted by the IOL and those that refract directly to the retina.[3]

"When I first started performing cataract surgery, we were implanting PMMA lenses, and dysphotopsias didn't seem to be an issue," recalls Dr. Tsai. "Then, as we got to the hydrophobic acrylic implants with the square edge to prevent the posterior capsule opacification, there was an increase of dysphotopsias. There's some thought that negative dysphotopsias have to do with the square edge and how it reflects light, creating an illumination gap. I think manufacturers are starting to round the edges more or use different materials with different refractive indexes to try to decrease this kind of illumination gap."

Dr. Masket says there's no doubt that PD are related to the IOL. "Not one IOL is manufactured in the United States today without some form of a square edge, and the square edge is hard to get rid of because it delays and inhibits PCO so people don't want to get rid of the square edge," he says. "It's also related to the index of refraction of the IOL. The higher the index of refraction, the greater the surface reflectability and the greater the units of PD. If you take a lens with a higher index of refraction and exchange it for one with a lower index, you'll cure between 85 and 90 percent of those patients with PD."

However, Dr. Masket believes negative dysphotopsias are related to the IOL's position in the eye. ND hasn't been reported with ciliary sulcus-, anterior chamber-, or scleral suture-fixated IOLs.[4] "It's not the material," he says. "It's not the edge design. It's not the size. It's really the position in the eye. There's a carload of evidence that if you take the very same lens that's sitting in the capsule bag and inducing ND and you bring the optic out of the bag and move it forward (reverse optic capture) then we're going to cure the patient. Alternatively, if we put the lens in the sulcus, if it's a three-piece lens, symptoms will go away."

Unfortunately, dysphotopsias can happen to anyone, making it impossible to predict who will fall victim. However, suggestions within the literature have identified some patients who may be more prone to experiencing them.

"Looking at the literature, it's been suggested that some patients with larger eyes or more shallow anterior chambers might be more likely to notice dysphotopsias," says Dr. Tsai. One study found that ND scotoma was associated more commonly with short axial length and high IOL power and another study found correlation with high angle kappa, commonly observed in hyperopic eyes.[5,6]

"There's a greater incidence of dysphotopsias in people with migraine," adds Dr. Masket. "We also know that the incidence of ND is higher in females than males. There isn't evidence that shows race, geographic location or age differences, however, we also think that perhaps patients who have a more sensitive central nervous system and are more perceptive are more likely to have dysphotopsias. But the one chief problem is that we haven't developed an ability to tell preoperatively who's likely to suffer postoperatively."

Initial Management Strategies

There's no way to accurately prevent dysphotopsia but there are various ways to manage the symptoms, from reassuring patients to surgical intervention.

• ***Listen to patients.*** Management strategies differ for both PD and ND, but the first step for both is to acknowledge your patient's concerns, say surgeons.

"I think it's very important how we approach these patients because the dysphotopsias occur when everything else is perfect," Dr. Masket says. "So the patient complains of seeing disturbances, and yet the surgeon looks at his or her work and this eye looks perfect, and many surgeons have kind of poo-pooed the patient's complaints, sending them to neurologists

and psychiatrists with no resolution. And that's a very unfortunate thing because the symptoms are real and the patient deserves the opportunity to have the condition discussed.

"It's very important that they're made to understand that there isn't anything wrong with them," he continues, "and that the surgery was perfect but these are optical phenomena we haven't completely figured out as of yet, but that we do have ways that can help them."

Dr. Tsai makes sure to counsel patients that neuroadaptation can take up to a year in some cases. "I use a lot of reassurance to the patients and continue to follow them until their symptoms improve," she says. "Patients need to understand this is a fairly common phenomenon that often improves. They need to know their surgeon is supportive. Reassuring them that this is normal and the rest of their eye is fine is important. I try to encourage them to focus on how improved their vision is."

• ***Conduct diagnostic exams.*** "When a patient complains of dysphotopsias after cataract surgery, you have to start by making sure to rule out any ocular pathology that may be causing the symptoms, especially retina problems," advises Dr. Tsai. "We check their vision and dilate them to evaluate the posterior pole. Underlying refractive error and tear film abnormalities can also be contributing to visual complaints. I try to maximize their vision by working on their tear film and making sure they have no underlying refractive error."

If pathology is excluded, ND can be measured with visual field testing, says Dr. Masket. Some have studied the incidence of ND with a Goldmann perimeter, he says, while he has personally used a Haag-Streit Octopus 900 perimeter which has a Goldmann module. Dr. Masket and colleagues published on this topic in 2019, plotting the ND scotoma on visual fields.[7] They found the ND scotoma to be far greater in extent when both eyes are fully open than when a peripherally occluding contact lens was applied to the fellow eye. "This phenomenon offers an understanding of why patients with ND may be more symptomatic than can be explained by the ND scotoma under monocular vision testing with full occlusion of the contralateral eye," they wrote. "However, under binocular VF testing, one can easily note that the scotoma is large enough to interfere with visual function in the temporal field of the involved eye(s)."

"One of the first things I do when I see the patient initially with these complaints is to ask them to cover their fellow eye with their hand, and very often the symptoms improve," Dr. Masket says. "Patching takes the symptoms away, but when the patch comes off, their symptoms return. I've also tried a peripherally opaque contact lens on the fellow eye and patients have improved, but most patients don't like how it blocks their vision, even though it works."

• ***Dilation drops.*** How the patient responds to dilation can also confirm the dysphotopsia diagnosis.

"One of the things that's interesting about ND is that the patient's symptoms almost invariably will be improved when we dilate the pupil," says Dr. Masket. "If your patient has been referred for symptoms of ND you can dilate the pupil and re-question the patient on whether the symptoms seem better or worse. With ND the symptoms will improve with dilation and worsen with constriction, which is the opposite of PD. PD can be helped by making the pupil smaller and worsened by making the pupil larger. Sometimes the ND and PD symptoms can overlap, so by dilating the pupil it helps us discern if their symptoms are more negative or positive.

"We can put them on dilute topical pilocarpine or brimonidine and either of those agents make the pupil smaller and to a great extent help the patient," continues Dr. Masket. "In my experience, the PD patient tends to be more tolerant of the problem than the ND patient because the ND patient loses a piece of their visual field and that seems to be really disconcerting, whereas the PD symptoms aren't constant—it varies with the lighting conditions so they may not be as bothered."

Surgical Interventions

Often, just knowing that nothing is wrong and they're likely to get better is enough for the great majority of patients and no further action is needed, say surgeons.

"I'll offer, 'Well, if it's really a bother, down the road (after a year or so) there's always the option of doing a surgical intervention like an IOL exchange, although I can't promise it will completely resolve your symptoms,'" says Dr. Tsai. "However, patients often say, 'No, it's not that bad, it's getting better,' and they're very happy to wait. They just want to be reassured that there's no other ocular pathology they need to be concerned with. They often just notice the dysphotopsias but aren't so severely affected by the symptoms that they would choose a surgical intervention."

Dr. Tsai only recalls two patients in 20 years who needed a surgical intervention. In one case she implanted a silicone piggyback IOL, and in the other she exchanged the original acrylic IOL for a silicone IOL. "Both procedures were successful, but I really try to avoid rushing into additional procedures if possible in the hopes that the patients will neuroadapt to the dysphotopsias," she says.

"If I were to do a surgical intervention (for ND), I would consider a reverse optic capture of the IOL," she says. "There's a thought that if the lens is moved more anteriorly in the eye, then that could help decrease their symptoms. In a reverse optic capture, you would lift the optic above the capsulorhexis, but you leave the IOL haptics in the capsular bag. That might cause a refractive change, however, and make the patient more myopic."

Dr. Masket also agrees he would

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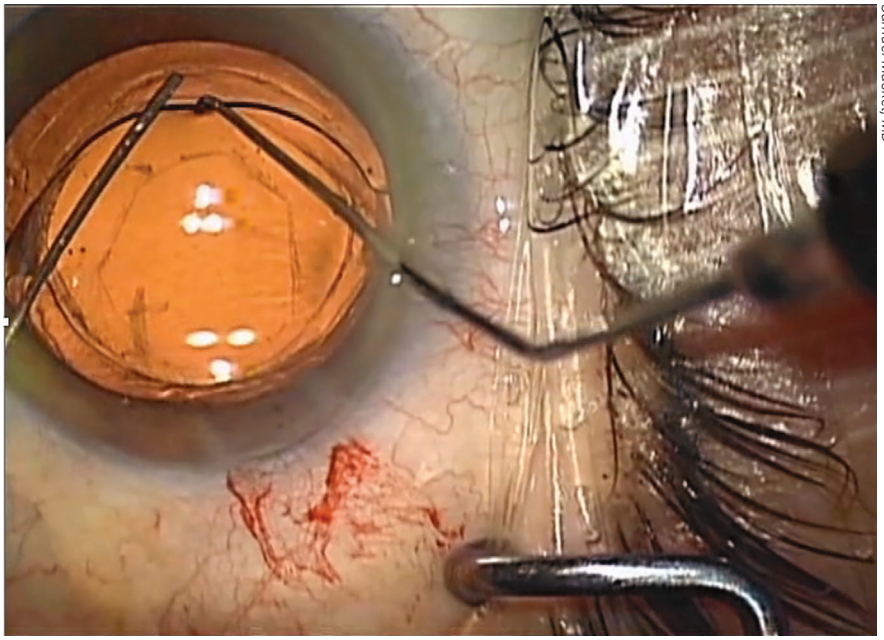

Samuel Masket, MD

In reverse optic capture, the optic of the IOL is lifted above the capsulorhexis, while the haptics remain in the bag. Studies have shown that when an IOL is moved anteriorly in the chamber, the symptoms of negative dysphotopsias subside.

consider reverse optic capture, but says there are downsides. "If a patient was highly symptomatic for ND in their first eye, I would do a primary reverse optic capture in their second eye—implanting the lens in the bag but at the end of the surgery I pop the optic in front of the capsule," he says. "That worked 100 percent of the time for me in patients who are highly symptomatic in the first eye, but there's a downside to it.

"The downside is that it changes the optical power a little bit, which isn't a total disaster," he continues, "but with the optic out of the bag, there's a very rapid onset of fibrotic PCO."

For those who fail to adapt to PD and don't respond to conservative treatments, IOL exchange to PMMA, silicone or copolymer IOLs in the capsular bag or ciliary sulcus have been reported to be successful overall.[8] In that study, Dr. Masket and his co-authors reported their outcomes with IOL exchange for chronic PD between 76 and 88 percent with both silicone and co-polymer IOLs when exchanged for hydrophobic acrylic IOLs as the inciting device. When square-edged acrylic IOLs were the inciting PCIOL, then the success rate from acrylic to silicone was 87 percent and from acrylic to co-polymer was 88 percent.

Dr. Masket says reinvented IOLs with capsulotomy fixation may ultimately provide the resolution needed for ND symptoms. He notes three IOLs currently in use in Europe: the Tassignon (Morcher) and Femtis (Oculentis) and one of his own design, the Masket 90S IOL (Morcher).

"Obviously physicians would like an IOL that doesn't produce dysphotopsias, as would the patient," Dr. Masket says. "The problem is that our present style of surgery to place a lens inside the capsular bag is what is associated with ND and it's only when we bring the optic anterior to the level of the capsule that the patient won't have any symptoms. So ideally there needs to be a groove on the anterior optic edge to capture the anterior capsulotomy and the IOL has to have a low index of refraction, which would reduce the incidence of either PD or ND. The downside (of the lens I've designed) is that it requires a perfectly sized and positioned anterior capsulotomy, so you'd need an automated capsulotomy whether by laser or other device in order to get that lens perfectly centered."

More Work to be Done

Much has been learned about dysphotopsias since they first became prevalent, but for Dr. Masket, it's ND that still has so many unanswered questions. "We know that ND is multifactorial and could benefit from IOL design, but there are so many more factors about ND that are poorly understood," he says. "Why does it occur in more left eyes than right? Why is it greater in women? There's a central nervous system connection not explained by any simple theory and we'd like to conduct functional MRI studies to determine what's going on in the brain when a patient sees negative dysphotopsias."◀

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DISCLOSURES

Dr. Masket is the designer of the Masket 90S IOL from Morcher and receives royalties from Haag-Streit. He is also a consultant for Ocular Therapeutix and CAPSULaser. **Dr. Tsai** has no disclosures.

TREATING FLOATERS: THE PROS, CONS AND TECHNIQUES

Some retinal surgeons are modifying their stance on treating floaters in certain symptomatic patients.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

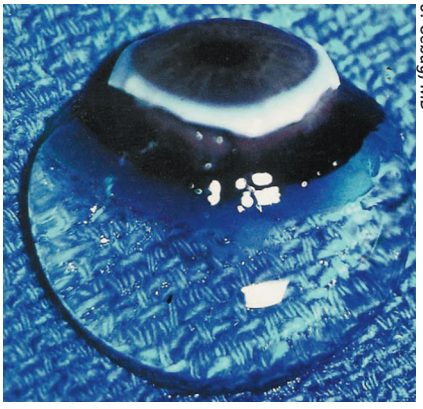
Floaters are a common complaint of patients of all ages, often caused by myopia in younger patients, and posterior vitreous detachment in older people. Until recently, vitreous floaters weren't viewed as something to be treated, and patients just had to cope with them as best as they could. Here, retina specialists discuss the sometimes controversial topic of actually treating these annoying, but sometimes debilitating, opacities.

Changing Attitudes

"Historically, floaters were dismissed by ophthalmologists, and I was one of those doctors for a very long time," says Jerry Sebag, MD, FACS, senior scientist at the Doheny Eye Institute/UCLA in Pasadena. "This stemmed from a lack of understanding of the origin of patient complaints and a lack of the ability to clinically measure things to characterize the condition as mild, moderate or severe. We didn't have those tools and were therefore left to determine whether an individual claiming disturbance by floaters was justified or overreacting. About 15 years ago, I started listening to these patients, and I started to believe them."

"I realized that we need to begin considering floaters a disease in some people," Dr. Sebag adds. "Many people have floaters that are inconsequential, but there are also many people who are debilitated by the opacities that induce floaters. 'Floaters' is a term that's misused. It's mistakenly used to refer to structures within the eye, but floaters are not structures. They're a visual phenomenon that is created by opacities within the vitreous. When you use ultrasound to image the structures within the eye that cause the visual phenomenon of floaters, we use the term 'echodensity,'" he adds.

To further clarify things, Dr. Sebag coined the term "vision degrading myodesopsia" to refer to patients who have clinically significant vitreous floaters.[1] "This term doesn't roll off your tongue easily, but it sure sounds like a disease. And that's what's needed to stimulate the paradigm shift in our perception that must occur if we're going to help those people who are afflicted, in many cases severely," Dr. Sebag says.



J. Sebag, MD

Figure 1. Intact vitreous body from a 9-month-old girl is still attached to the anterior segment after dissection of the sclera, choroid and retina. The exquisite gel state of this vitreous body maintains its shape, despite being situated on a surgical towel exposed to room air.

In collaboration with acoustic engineers in New York, and with Dr. Alfredo Sadun at the Doheny Eye Institute in Pasadena, Dr. Sebag developed metrics that he now uses on a routine basis to evaluate patients who complain of floaters. The first metric measures the density of vitreous using quantitative

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Dr. Lim has no financial interests to disclose. **Dr. Sebag** has IP interests in the patents for quantitative ultrasonography and Nanobubble therapy.

Clement Trempe, MD

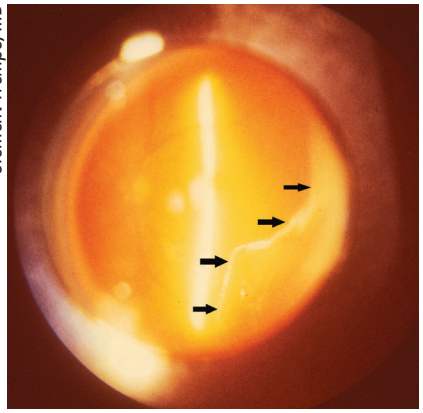


Figure 2. Preset lens biomicroscopy of the left eye in a patient with posterior vitreous detachment shows the posterior vitreous cortex (black arrows) separated away from the posterior pole (optic disc and retinal blood vessels seen to the left). The "sigmoid" configuration of the collapsed vitreous body is due to the effects of gravity on the superior vitreous body, causing it to descend inferiorly.

ultrasonography.[2] "Ultrasound used to be a mainstay in evaluating the eye, but ever since optical coherence tomography came along, people tend to default to that rather than use ultrasound to image the structures within the eye. OCT is excellent for the retina, but it's poor to evaluate vitreous, and so ultrasound has filled that void. We worked with acoustic engineers and developed ways to quantify ultrasound imaging to assess the severity of the structural changes within the vitreous body that cause the visual phenomenon of floaters," he adds.

The other useful metric was to measure contrast sensitivity.[3,4] "While this has been available for many years, ophthalmologists tend not to routinely do that test. Instead, we rely on visual acuity as a measure of the person's ocular health. While that's useful for evaluating some diseases, it's not good in evaluating the visual impact of vitreous opacities. Contrast sensitivity, however, is a very useful way to measure the impact of vitreous opacities on vision and to explain why people are so unhappy," Dr. Sebag describes.

Treatment

According to Jennifer I. Lim, MD, director of the Retina Service at University of Illinois Health, there are two schools of thought on how to surgically treat floaters. First is a core vitrectomy where the vitreous gel and any visible opacities are removed centrally. Second is the complete vitrectomy with creation of a PVD. "I perform complete vitrectomies, and I induce a PVD if there's not one already," she says.

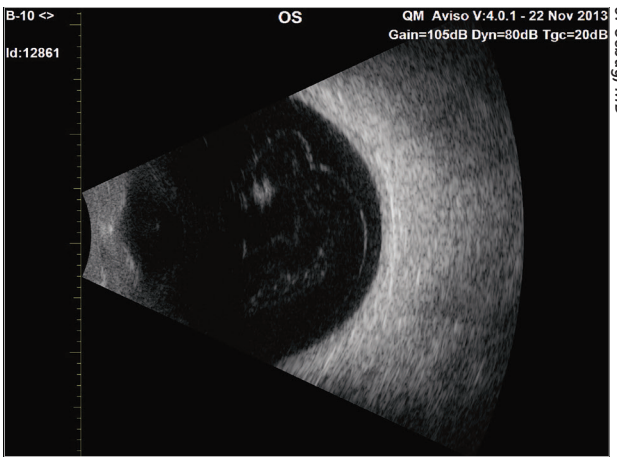
Dr. Lim mentions that floaters originate in some patients who are very nearsighted or have other vitreous abnormalities, from vitreous degeneration and liquefaction. "In the other group of patients, where the PVD has occurred, the floaters result from collapse of the vitreous gel and opacities within the gel," she says. "Floaters may result from liberated tissue/blood/pigment as the vitreous separates from the underlying retina and can also result from a retinal tear, or from a retinal detachment if it occurs during the patient's PVD. Of course, the risks of inducing a retinal tear are higher while you create a PVD surgically especially in highly myopic eyes with thin retinas. However, if you don't induce a PVD, over the course of time, that patient will eventually develop a PVD, and when he or she does, that patient will develop floaters, in addition to being at risk for a retinal tear or a retinal detachment at that time. Thus, I like to create the PVD in the operating room where it's very controlled, and then not have to worry about the patient undergoing a PVD in the future and getting floaters back again."

Dr. Sebag has studied this and found that it occurs in only 14.1 percent of individuals who have undergone limited vitrectomy without intraoperative PVD induction.[5] None of those cases developed retinal tears or detachments.

Dr. Lim adds that, "Once you navigate the psychosocial and physical exam aspects of it, it's a reasonable procedure to do. I'm quite pleased that my patients are doing well. This includes both the older patients who have the PVD, as well as the younger ones who just have the liquified vitreous and are very bothered by the floaters. Some of them—who have floaters in both eyes—after they have one eye done, want the other eye done as well because they're so happy to be free of floaters. I have patients who are several years out from surgery, and they're quite pleased with their outcome."

If a patient has a cataract and vitreous floaters, she performs a combined case and has an anterior segment surgeon remove the cataract. Then, she performs the vitrectomy for the floaters.

Dr. Sebag's procedure of choice is a limited vitrectomy. "I leave 3 or 4 mm



J. Sebag, MD

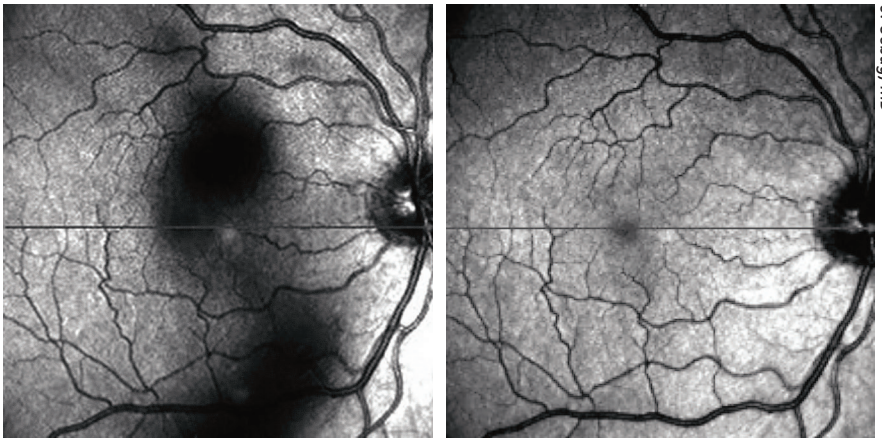
Figure 3. B-scan ultrasound demonstrates posterior vitreous detachment and central vitreous echodensities. Both interfere with photon transmission to the retina, resulting in degradation of contrast sensitivity from untoward light scattering.[1] The large echodensity towards the top of this image might be amenable to YAG laser vitreolysis, while the other densities and the posterior vitreous cortex are probably best treated by vitrectomy.

of gel vitreous behind the lens intact to mitigate against cataract formation, and if the patient doesn't have a PVD, I don't induce one surgically, to minimize the risks of retinal tears and detachments but also to limit the increase of intravitreal oxygen levels that occurs following vitrectomy," he says. "It's the increase of O_2 in vitreous that causes the changes in the lens that result in cataract formation. So, limited vitrectomy was developed in recognition of the fact that doing vitrectomy for floaters needed to be as safe as possible. To increase the safety profile, I avoided inducing a PVD and hoped that, as a result, the incidence of retinal tears and detachments would be lower. It turns out that this only occurs 1.5 percent of the time, meaning that limited vitrectomy is 98.5-percent safe," he says.

In 2018, he published a study of 195 subjects who were treated with limited vitrectomy.[6] This study had a high success rate as determined by quantitative ultrasonography and by measuring contrast sensitivity. "Concerning the latter," says Dr. Sebag, "in 139 consecutive cases who preoperatively had an average degradation in contrast sensitivity of 91 percent in comparison to controls, contrast sensitivity was normal in each case within a week of limited vitrectomy, and that was sustained for months and years thereafter. Cataract surgery was required in only 16.9 percent of cases, and retinal detachments only occurred in 1.5 percent of cases.

"Moreover, the patients were extremely happy, and we also documented that quantitative ultrasonography was significantly better in this series of patients," Dr. Sebag adds. "The complication rates were very acceptable. This study showed that limited vitrectomy was highly effective and safe."

Studies have also shown that, after limited vitrectomy in patients who are unhappy after cataract surgery with multifocal IOL implantation, contrast sensitivity improved, in spite of the multifocal intraocular lens.[7] Dr. Sebag therefore recommends vitreous evaluation in patients who are unhappy with multifocal pseudophakia and that there be consideration of limited vitrectomy for these unhappy patients.



J. Sebag, MD

Figure 4. Opacities in the vitreous body cast shadows on the retina (left image) that patients perceive as "floaters." These are displaced with head movement and ocular saccades, exhibiting characteristic movement dynamics ("lag" and "bounce") owing to the viscoelastic properties of vitreous. Following limited vitrectomy, the central vitreous is clear (right image), floater symptoms cease and contrast sensitivity normalizes.[6-8]

He has performed more than 300 limited vitrectomies on all types of patients. "So far, limited vitrectomy has been found to be more cost effective than amblyopia therapy, cataract surgery, and retinal detachment repair,"[8] he says.

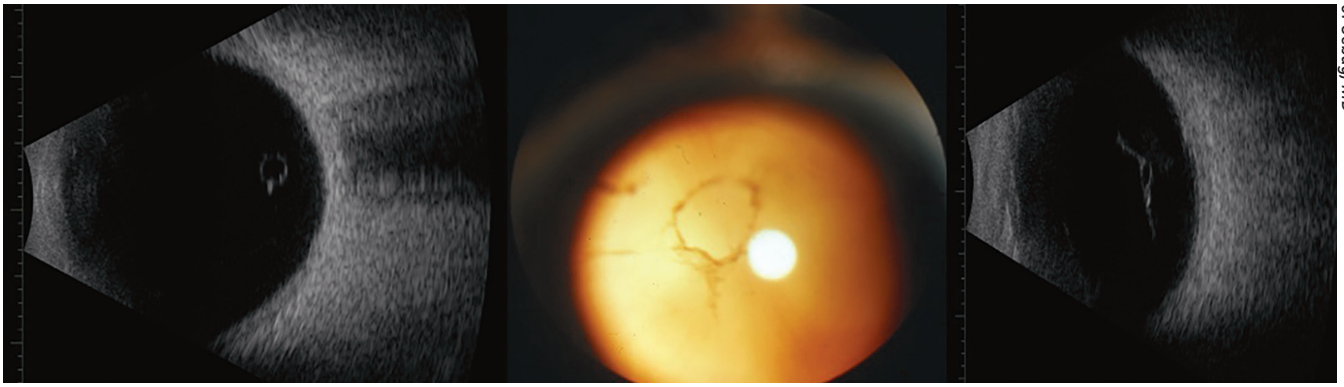
YAG laser vitreolysis (YLV) is an alternative to vitrectomy, because surgery isn't for everyone. "In spite of being highly skeptical of YLV in the past, I've opened my mind to the possibility that YLV has a role in certain cases," says Dr. Sebag. "Whereas YLV has been done for years all over the world, it hasn't been embraced by the vitreoretinal surgery community. It's being done by general ophthalmologists, and I wonder whether it might be embraced by the vitreoretinal community and perhaps be done with greater precision and efficacy if it could be shown to be effective in a subgroup of individuals."

He believes that YLV will be somewhat successful, but not in all patients. "The reason is that there's more than one cause for vision-degrading myodesopsia and vitreous floaters," he notes. "The leading cause is a PVD, which tends to be the case in older individuals. I think that in those individuals, it will turn out that YAG laser isn't effective, except for the subset of people who have a disturbing Weiss ring or a particularly prominent central vitreous opacity in whom YLV might be effective, at least subjectively by questionnaire evaluation and perhaps also by contrast sensitivity measurements."

He believes that patients with myopic vitreopathy, which is the second leading cause for vitreous floaters and vision-degrading myodysopsia,[9] may be good candidates for YAG laser treatment. "These people tend to be younger and don't have a PVD, so those may be the individuals who should be treated with YAG laser. We're currently conducting a prospective clinical trial of YLV and hope to report the results in the not-too-distant future," he says.

The Future

Other technologies are currently being considered for treating vitreous floaters. "Picosecond and femtosecond lasers may prove to be more effective than YAG laser, especially if the treatment can be localized with 3D imaging guidance of the laser energy,"



J. Sebag, MD

Figure 5. Weiss Ring imaged by ultrasonography (left) and fundus photography (center). Image on the right shows Weiss Ring within the detached posterior vitreous cortex.

says Dr. Sebag. "That would help YLV, as well, but with more powerful lasers, we will probably be able to ablate the opacities rather than just break them down, which is what's occurring now with the YAG laser. Pharmacologic vitreolysis may also play an important role in chemically breaking down the aggregates of collagen that are in the vitreous body that cause the shadows that result in the visual phenomenon of floaters and degradation of contrast sensitivity. I'm very excited about the possibility of developing drugs and injecting them into the vitreous body to treat vitreous floaters and vision degrading myodesopsia.

"Following the recent anti-VEGF experience," Dr. Sebag continues, "we're all comfortable injecting drugs into the vitreous body, so it wouldn't be that hard to get the community to accept pharmacologic vitreolysis as a treatment paradigm for vision degrading myodesopsia, but we need to develop the right drugs and use them at the right dose, so a lot of work needs to be done in that regard."

Another approach is being developed at the University of Ghent in Belgium using nanoparticles that are specifically designed to adhere to the opacities within the vitreous body that are causing floaters and vision-degrading myodesopsia.[10] "After injecting the nanoparticles, a low-energy laser is used to treat the vitreous body, which doesn't have to be targeted because the nanoparticles chemically adhere to the opacities and preferentially absorb the laser energy, creating localized nanobubbles that break up the membranes and aggregates of collagen that are causing the floaters and vision degrading myodesopsia," explains Dr. Sebag. "This has been developed *in vitro* and has been tested in rabbits *in vivo*.[10] It's been shown that the laser energy levels that are required are 1,000 times less than what's currently being used for YLV. I would like to see it developed further for the treatment of patients with vitreous floaters."

Then, there is an optical approach. "If we understood the optics and physics of how light is interacting with the structures within the vitreous body that are causing floaters and inducing vision-degrading myodesopsia,[11] perhaps that could be corrected with an optical apparatus that counteracts the untoward effects of light scattering, which degrade contrast sensitivity. If we neutralize that, maybe we could decrease the symptoms and lessen the impact by treating optically," Dr. Sebag says.

Dr. Sebag concludes that, "It's not often that you come across an unmet medical need, where simply opening your mind and heart not only opens new diagnostic and therapeutic avenues, but resonates with patients. They feel ignored, they feel dismissed, they sometimes even feel insulted by the approach that we've taken up until now. But, as is always the case with increased knowledge and good science, we become armed with the tools that will help us understand the plight of our patients and enable us to develop better ways to evaluate what's happening to them, as well as more effective and safer ways to treat them." ◀

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A CLOSER LOOK AT SAME-DAY SURGERY

Proponents say the approach can save patients, providers and the health-care system time and money.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

While the current sequential approach to cataract surgery is still the standard, the emergence of same-day, bilateral cataract surgery has sparked considerable interest, raising questions about its efficacy, safety and overall patient outcomes. There are a number of advantages associated with same-day, bilateral cataract surgery, also referred to as immediately sequential bilateral cataract surgery (ISBCS), including enhanced patient convenience, reduced health-care costs and expedited visual rehabilitation. Patients may experience shorter overall recovery times and decreased postoperative visits, leading to greater patient satisfaction. However, there are also potential concerns that may impact a surgeon's decision when determining the best approach for their patients. These include surgical complications, refractive considerations and reimbursement challenges.

Here, we'll explore the pros and cons of same-day, bilateral cataract surgery, and engage in a nuanced discussion of the complexities surrounding this approach. Experienced surgeons offer their perspectives and advice to help their colleagues navigate this debate and make informed decisions that are in the best interest of their patients and practice.

Why ISBCS?

Proponents argue that same-day, bilateral cataract surgery offers advantages for patients, ophthalmologists and the health-care system as a whole. Quicker binocular vision recovery, increased surgeon efficiency, decreased postoperative visits and decreased patient time spent in a surgery center are all benefits of this approach, says Sloan Rush, MD, of Amarillo, Texas.

For patients with limited mobility, transportation challenges or busy schedules, the ability to undergo surgery on both eyes in a single day can significantly improve their overall experience. Additionally, this surgical option may alleviate anxiety and apprehension associated with multiple surgeries, which could benefit patient satisfaction and outcomes.

"With two separate surgery dates and associated postop visits, it can be upwards of eight or more trips to the doctor's office. That number can be significantly reduced with bilateral same day surgery," notes Derek DelMonte, MD, of Greensboro, North Carolina, who also highlights the potential burden of additional travel. "Many patients travel a good distance for this surgery, particularly those who live in more rural areas. The likelihood of a car accident/injury on the trips was higher than the likelihood of a complication from bilateral same day surgery."

Faster visual recovery is another reason to consider ISBCS for eligible patients, some surgeons say. By performing surgery on both eyes on the same day, patients can achieve optimal visual acuity in a shorter timeframe. This improvement in vision enhances overall quality of life and enables patients to resume daily activities sooner, minimizing the disruption caused by prolonged recovery periods.

"For patients with high preop prescriptions, the time spent with anisometropia after one eye is operated on can be very bothersome," says Dr. DelMonte. "Some patients experience dizziness/nausea due to the high level

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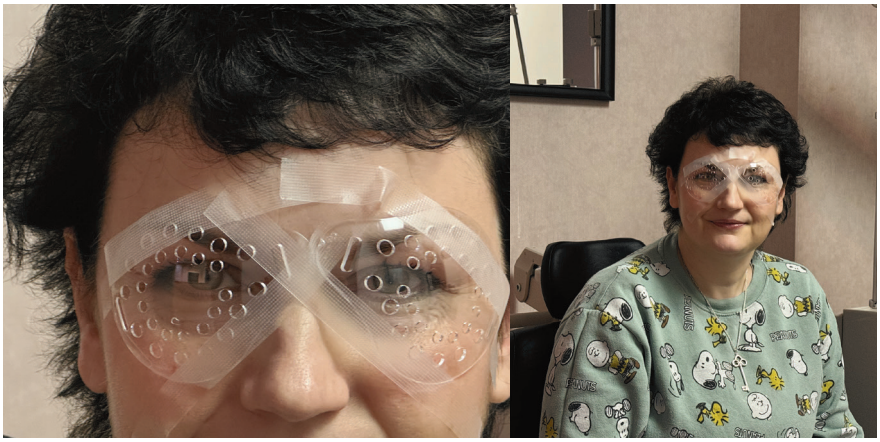

Derek DelMonte, MD

Figure 1. In addition to identifying good candidates for bilateral same day cataract surgery, surgeons may incorporate small changes to pre- and postop routines to help achieve successful outcomes for both the patient and surgeon, for example, using clear shields postoperatively.

of anisometropia and many find it difficult to perform their daily tasks such as work and hobbies."

The impact can be even greater for older patients with a higher risk of falls/instability, he adds, while noting that, "this time also delays the brain's ability to learn how to adjust to the 'new normal' of their vision. This neuro-adaptation is much faster if both eyes are performed at the same time."

The time spent with only one eye done can be frustrating for the patient and actually make it more difficult for some individuals to adjust to the final outcome once the second eye is complete, emphasizes Dr. DelMonte.

ISBCS can reduce costs for patients (surgery cost, travel expenses, time out of work, etc.) and the health-care system (i.e., less OR time, fewer visits). "This cost savings can add up to large amounts for the overall health-care system considering the number of people undergoing cataract surgery in the U.S. (and world) yearly," says Dr. DelMonte. "As many are still working, the overall saving to the general economy could also be taken into account as time away from work is lost productivity."

Safety Considerations

Some surgeons may be hesitant to use this approach for several reasons, including safety and refractive concerns. One of the often-heard arguments against bilateral same-day surgery, notes Dr. DelMonte, is the risk of a bilateral infection (endophthalmitis).

"If a patient were to experience a bilateral complication on the same day, it could have a much more devastating impact on the patient than if only one eye had the complication and could be rehabilitated prior to the second eye surgery," he notes. "This is perhaps more likely in the case of TASS (toxic anterior segment syndrome) which is an inflammatory complication after surgery that can look like endophthalmitis but happens in 'outbreaks' that can impact a whole day or part of a day of surgery."

There's still some controversy regarding the most common cause of these outbreaks; however, many believe they are related to contaminants in the surgery pathway (instruments/cleaning supplies, etc.) that impact more than just one patient, says Dr. DelMonte.

While potential risks should always be considered prior to any procedure, recent years have seen a significant decrease in the risks associated with same-day, bilateral cataract surgery. Advancements in incision size, equipment and infection prophylaxis have made the overall risk of complications very low, according to Dr. DelMonte.

"The risk for bilateral blinding complication is still extremely low," adds Dr. Rush. "Using intracameral antibiotics such as moxifloxacin (and not vancomycin due to risk for hemorrhagic occlusive retinal vasculitis [HORV]) decreases the risk for endophthalmitis to 1 in 10,000 or less. Therefore, this complication occurring consecutively is exceedingly rare."

It's also important to note that most surgeons, including Dr. DelMonte, advocate for a completely separate procedure from start to finish with the exception of the patient not leaving the operating room between surgeries.

"This means after the completion of the first eye, the patient's drapes are removed, the eye is cleaned and when the patient would normally be leaving the room, the whole OR team prepares for a completely new procedure with new equipment, new drapes, new preop prep, etc.," he explains. "No steps should be skipped to maintain a low risk of bilateral complications. It should also be noted that if a complication occurs during the first eye, the second is postponed to a different day."

Vallejo, California, surgeon James Carolan reiterated the rarity of these complications when guidelines are followed and appropriate safety measures are taken. "Yes, there are risks but if you're fastidious about working with reliable vendors, separating by lot number and following the principles put forth by the International Society of Bilateral Cataract Surgeons, that risk is very small," he says. "Cases of TASS or bilateral infection are more likely to occur when the workflow is changed, vendors change or something else out of the ordinary happens."

There are also refractive considerations to take into account before making a decision on the best surgical approach. "While our ability to hit a refractive target with surgery is remarkably good, there are still cases that end up more myopic or hyperopic than anticipated," says Dr. DelMonte.

If this happens in the first eye,

ophthalmologists can adjust their approach prior to performing surgery on the second eye. "In patients in whom certainty with lens selection is challenging, for example post-radial keratotomy patients, it can make sense to avoid same-day surgery to better help us with the second eye," says Dr. DelMonte.

Another case where same-day surgery may not be the best option is in patients who are contact lens dependent, such as those with corneal ectasia. "These patients will often need to be re-fitted with a new contact lens prescription prior to gaining visual improvement from cataract surgery," explains Dr. DelMonte, who recommends waiting for full rehabilitation of the first eye before proceeding with the second eye's surgery. This can help avoid bilateral visual impairment for a period of time between surgery and contact lens refit.

The risk of a postoperative surprise in refraction is improving as the newest formulas continue to better estimate effective lens position and account for posterior corneal contributions to refraction, he notes.

Since the vast majority of surgeons perform surgery within the postop healing period of the first eye, they'll rarely get a final refraction from the first eye before operating on the second eye. "The question then becomes, when would you adjust the second eye based on incomplete data from the first eye? The answer is really only if there is a very large error, which is exceedingly rare," says Dr. DelMonte.

"Some may argue that the risk of having to do a bilateral lens replacement (or laser refractive enhancement) is enough to avoid bilateral surgery; however, the number of times this may be needed does not necessarily outweigh the benefits to so many," he argues. "By simply avoiding patients at the highest risk for refractive surprise, we may be able to minimize this risk significantly."

Dr. Carolan underscores the importance of patient selection for successful same-day, bilateral cataract surgery. "Not every patient will be the right fit, and not just because of health-related issues," he notes. "You also need to consider a patient's social situation and support system. Ask them about their occupation and home life."

"How are they going to do during those first few days when both eyes are blurry? Do they have the necessary support? Will they have difficulty with postoperative compliance? The entire patient must be considered when determining if they're right for same-day, bilateral cataract surgery," Dr. Carolan emphasizes.

There is also the possibility for lens errors with ISBCS; however, simple changes to time-out and preparation for bilateral same-day surgery can help mitigate this risk, according to Dr. DelMonte.

"For example, most will perform two separate time-outs, one prior to each case. Leaving only the IOL for the current surgery in the room and having color-coded IOL selection sheets (Blue for right eyes, Green for left eye or similar) which indicate the eye I am working on at the time all help," he says. "With these adjustments, I haven't found an increased risk of wrong-IOL implantation in these cases."

Reimbursement Challenges

Despite the potential benefits, reimbursement remains a significant barrier to the widespread implementation of same-day, bilateral cataract surgery. In fact, Drs. Carolan, DelMonte and Rush agree that this is the main reason why it hasn't been more fully adopted by practices.

"I believe the decrease in reimbursement is the largest inhibitor to widespread adoption," says Dr. Rush. "The bilateral modifier 50 indicator from Medicare and other insurances dates back to the 1970s and only permits for 50 percent of the allowable for the fellow side of any body part operated on, regardless of if it being an ear, an eye or a knee.

"This decrease in reimbursement generally results in a net loss of revenue for the second eye for the surgery center, making it financially unviable," he continues. "Further, the advances in surgical techniques make this reimbursement ruling obsolete. When adhering to published guidelines for ISBCS, the safety of ISBCS is comparable to delayed sequential bilateral cataract surgery."

Dr. Rush's practice routinely performs next-day sequential bilateral cataract surgery (NDSBCS) on almost all patients that don't have a contraindication (80+ percent of all cataract patients), which allows for full reimbursement and confers some (but not all) of the advantages of ISBCS, he explains.

"More individuals are being trained in this approach; however, when entering practice they're faced with a reimbursement structure that won't allow them to perform the procedure, unless they're working in the VA or a capitated system," notes Dr. Carolan. "The time is coming for this idea to become more widespread, but the main issue holding us back is reimbursement."

Patient Experiences

A cross-sectional study—conducted at Kaiser Permanente—evaluated patient experience and satisfaction with same-day bilateral cataract surgery versus DSBCS.[1] Study authors, including Dr. Carolan, sent a survey to patients who received immediate sequential bilateral cataract surgery (ISBCS) (n=1,818) and DSBCS (n=1,818) between 2017 and 2019.

The research showed that patients who opted for ISBCS were more likely to choose this approach again and recommend it to a family member or friend. While convenience was the leading reason patients chose ISBCS (65 percent), surgeon recommendation was the primary reason patients elected for DSBCS (68 percent).

From his own clinical experience, Dr. Carolan finds that the majority of his patients are glad they had same-day, bilateral cataract surgery. "Where

you run into trouble is poor patient selection," he says. "I've been doing this long enough that I have a good idea who would benefit from the ISBCS option and are most likely to have a positive overall experience." He notes that he's currently performing ISBCS in approximately 30 percent of his patients. "I could do more, but I choose not to because I feel it's the right approach for my patients and practice," he adds.

Dr. Rush has also found that most of the patients at his practice who undergo ISBCS are pleased with the simplicity of only going to a surgery center once, the decrease in visits associated with postoperative care and the quicker bilateral vision recovery. "Most of these patients assume that everyone gets ISBCS as they did and are even surprised to learn that the majority have delayed sequential bilateral cataract surgery," he says.

"Those of my patients who have undergone bilateral same-day surgery are generally some of my most happy patients," adds Dr. DelMonte. "I do inform all up-front that this isn't necessarily what most of their friends/relatives may choose or qualify for, but for select patients it's a safe and effective procedure. I do spend a bit of time with the reason this isn't always offered, to fully inform them of the risks associated with this method, however most are very happy to be given this choice and gladly accept the offer."

Key Takeaways

Same-day, bilateral cataract surgery is a compelling option, offering a range of potential benefits alongside certain considerations. The convenience, faster visual recovery and potential cost-effectiveness of this approach make it an attractive choice for certain patients; however, it's essential that ophthalmologists weigh the advantages against potential drawbacks and individual patient factors.

"I recommend ISBCS for all routine, healthy patients in which there is both no financial reimbursement-barrier and no medical contraindication," says Dr. Rush. "Otherwise, we offer NDSBCS. The most common ISBCS candidates in our practice are patients seeking elective vision correction procedure with refractive lens exchange. These eyes are usually healthy, and the patient is paying out of pocket which eliminates all reimbursement barriers.

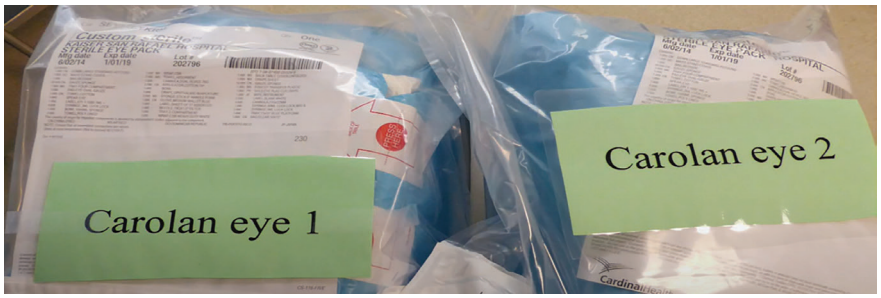

Figure 2. When performing same-day, bilateral cataract surgery, or ISBCS, all equipment should be separated and each eye should be treated as an individual procedure.

"In addition, the advent of office-based surgery (OBS) allows for an advanced beneficiary notice which allows for the center to compensate for the relative loss in revenue due to the bilateral modifier 50 ruling," he adds, while noting that patients with existing severe ocular co-morbidities should avoid ISBCS.

When asked what advice he would give to surgeons interested in trying this approach for the first time, Dr. Rush says they should be familiar with the published guidelines for excellence with ISBCS and start slowly with uncomplicated cases. Once confidence is gained, then it can be offered more routinely in select cases.

Dr. DelMonte emphasizes the importance of patient communication. "Have a good discussion about bilateral same day surgery with the patient and their family so they know the reasons to consider this, as well as reasons to decline if desired," he says. "And remember that just because you plan for bilateral same day surgery, doesn't mean you must proceed that way—know that plans can be changed if any difficulty arises during the day, and plan to discuss that possibility with the patient beforehand."

Same-day, bilateral cataract surgery can be a very safe and effective procedure for the majority of patients who have bilateral cataracts, according to Dr. DelMonte; however, the important thing to keep in mind is that it may not be best for everyone.

"Identifying those who may benefit the most while avoiding those at the highest risk is the true challenge," he says. "Additionally, surgeons must be honest with themselves about their personal complication rates (particularly beginning surgeons) and may elect to offer or not offer based on their comfort level with postoperative complication risks."

Dr. DelMonte believes that this approach will continue to gain favor over time. "I think fewer young surgeons are as familiar with the higher rates of complications cataract surgery had just a few years ago, and so are less gun-shy about trying this technique," he notes. "In order for more surgeons to adopt it in this country, however, the reimbursement issue will have to be fixed. The most common place to see bilateral same day surgery in the U.S. are in health systems that don't penalize the reimbursement, such as the Kaiser system, or the VA, and they've had great success with it."

"The increasing utilization of premium IOLs, self-pay and OBS will eventually make ISBCS the most common method of cataract surgery," predicts Dr. Rush. "But it may take another decade or more." ◀

1.Carolan JA, Amsden LB, Lin A, et al. Patient experience and satisfaction with immediate sequential and delayed sequential bilateral cataract surgery. Am J Ophthalmol 2022;235:241-8.

MASTERING NEW-TECHNOLOGY LENSES

Surgeons offer their top tips for working with the Apthera IOL and the EVO ICL.

LIZ HUNTER
SENIOR EDITOR

Since their approval by the FDA, the Apthera IOL (Bausch + Lomb) and the EVO+ ICL (Staar Surgical) have given surgeons new options for enhancing patients' vision. Their designs have the potential to fill a niche for patients who might otherwise be challenging to please or have characteristics that disqualify them from alternatives. Surgeons who have been working with these lenses since the clinical trials say they're useful assets in their armamentarium, so we asked them to share the lessons they've learned and techniques they've honed. Here's what they had to say.

Apthera IOL

Initially brought to market by AcuFocus before being acquired by Bausch + Lomb, the Apthera (originally called the IC-8) is a non-toric extended-depth-of-focus IOL for patients with up to 1.5 D of astigmatism. Meant to be implanted in the non-dominant eye, the Apthera uses small-aperture technology and is available in +10 D through +30 D in 0.5-D increments.

John Hovanesian, MD, a cornea, cataract and refractive surgeon at Harvard Eye Associates in Laguna Hills, California, took part in the FDA clinical trials for the Apthera. "I've been using it for approximately three years now, and I had a chance to use it even prior to that in El Salvador to experience it and see patients with it," he says. "It's a very unique lens that serves an important purpose that no other tool can fill. While it may not be for every patient, it's certainly for every surgeon. It's important enough, it's unique enough that everybody should know about how and where it works."

• ***On- and off-label candidates.*** Patients had to meet strict criteria to be included in the FDA study, which was designed for monovision in normal eyes. Another surgeon who was involved in the study, William F. Wiley, MD, medical director of the Cleveland Eye Clinic, says that not only did patients have success with the Apthera, but it was technically easier to implant than previous small-aperture options.

"Our practice was familiar with small-aperture optics, including the Kamra corneal inlay, which we found did well optically, but there were some technical challenges with it surgically," Dr. Wiley says. "It was hard to get it perfectly aligned or centered, and there were some biocompatibility issues with it being in the cornea. When we had the opportunity to have the same aperture optics, but now putting it into an IOL, it made it technically much easier as well as helped with biocompatibility. Now there aren't any issues because it's encapsulated within the intraocular lens."

Patients who are already familiar with monovision in their contact lenses are great candidates for the Apthera, Dr. Wiley continues. "Studies show that, for monovision patients, it's a great alternative. Patients who've had a lot of success with contact lens monovision were used to having some accommodation where, when they wore contacts, their natural lens had some accommoda-

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Dr. Dhaliwal is a medical advisor for STAAR Surgical. **Dr. Hovanesian** consults for Bausch + Lomb. **Dr. Vukich** is a consultant for Bausch + Lomb and a principal investigator/medical monitor in the Apthera clinical trials, and a medical monitor/senior medical advisor for STAAR Surgical. **Dr. Wiley** is a consultant for Bausch + Lomb and STAAR Surgical.

tion, and if the eye was targeted for -1, they'd still have natural accommodation that would give the full range of vision with contacts," he says. "But once you go to pseudophakic monovision, monofocal IOLs are so rigid as far as their depth of focus, that patients didn't really adapt as well. They always say they love monovision in their contacts, but they don't like it with the IOL. With the small-aperture, it gives true depth of focus, more similar to what patients might have experienced with their contact lenses where you target maybe a -1, but now that aperture can bring in that -1 for better near vision while maintaining some of the distance vision as well. So it tends to be more analogous to what they'd seen with a contact."

It's this distance vision 'x-factor' that surgeons say sets the Apthera apart. "With monofocal IOLs set for monovision you have to subliminally ignore (but sometimes consciously) the eye that's out of focus and use one eye for distance and the other for near," says John Vukich, MD, the founder and medical director of Summit Eye Care in Wisconsin, and a principal investigator in the clinical trials for Apthera. "You lose depth perception and binocularity with monovision. With Apthera, you maintain binocularity at distance. You don't have to alternatingly suppress one eye vs. the other. You maintain binocular summation or quality of vision, meaning that two eyes together in focus are better than one eye only.

"When I discuss this with patients I describe it as blended vision," he continues. "We don't call it monovision because that's not really accurate. There are many patients for whom they may have tried monovision with contact lenses and rejected it because it wasn't comfortable or they just couldn't habituate to it. Those patients do extremely well with the Apthera because they're not losing the binocularity. It's a great solution that patients do very well with."

However, now that the Apthera has been in clinical use for nearly two years, its usefulness beyond "normal eyes" is becoming apparent.

"The second personality of Apthera, if you will, is for the irregular eye," says Dr. Hovanesian. "This is really where most of these lenses get used, certainly in my practice. These are patients with keratoconus or radial keratotomy and highly irregular surfaces where there's not just an issue with cataract, but an issue with irregularity that you can't correct with anything but maybe a scleral or RGP lens. Here, we have a lens implant that can provide not only an improvement in uncorrected acuity but an improvement in best-corrected acuity because it gives them small-aperture optics."

Bausch + Lomb

The small-aperture technology of the Apthera IOL is meeting the needs of patients with both normal and irregular corneas, say surgeons.

Dr. Wiley echoes this experience. "Beyond what the FDA indications were, we also find that aperture optics can give a great solution for more unique situations," he says. "In particular, when someone's had radial keratotomy or has keratoconus, we can prove in the lane that they see better through a pinhole device and now we can offer that through small-aperture optics with an IOL. We've also found this niche application with irregular astigmatism that takes people who just weren't seeing well with typical correction now have the ability to have some of that best-corrected vision improved and we've been excited about that."

The pinhole mitigates some of the inherent aberrations or irregularities in the visual system experienced by those with RK, says Dr. Vukich. "One of the things that's really quite helpful is that many patients who've had RK have fluctuations in vision," he says. "They may have a different prescription in the morning than they do at night—there could be a 1.5 D of change over the day. With the Apthera, if we just set it for that endpoint, the depth of focus mitigates that fluctuation because the depth of focus eliminates that perception of quality change or perception of refractive correction.

Another off-label use for Apthera is bilateral implantation. "I've used it bilaterally, although it's indicated for unilateral use," notes Dr. Hovanesian. "The way I approach it is: when you have a patient with bilateral keratoconus, they want to be better in both eyes, so I'll implant Apthera in the more irregular eye first. Afterwards, I'll ask them to judge how much dimming they noticed and if they'd tolerate a similar amount in the other eye. If they feel positive about that, then I'll implant it in the other eye. I've done that a number of times now and so have other surgeons with good results because the gain in acuity offsets whatever dimming they experience. Apthera certainly can be used bilaterally."

• ***Preop considerations and targeting***. "You'll conduct the routine cataract/IOL preop testing, but you do have to be more mindful of certain things that wouldn't make them a good candidate, such as anything that may interfere with the optical pathway, including a central corneal scar, prominent vitreous floaters, any

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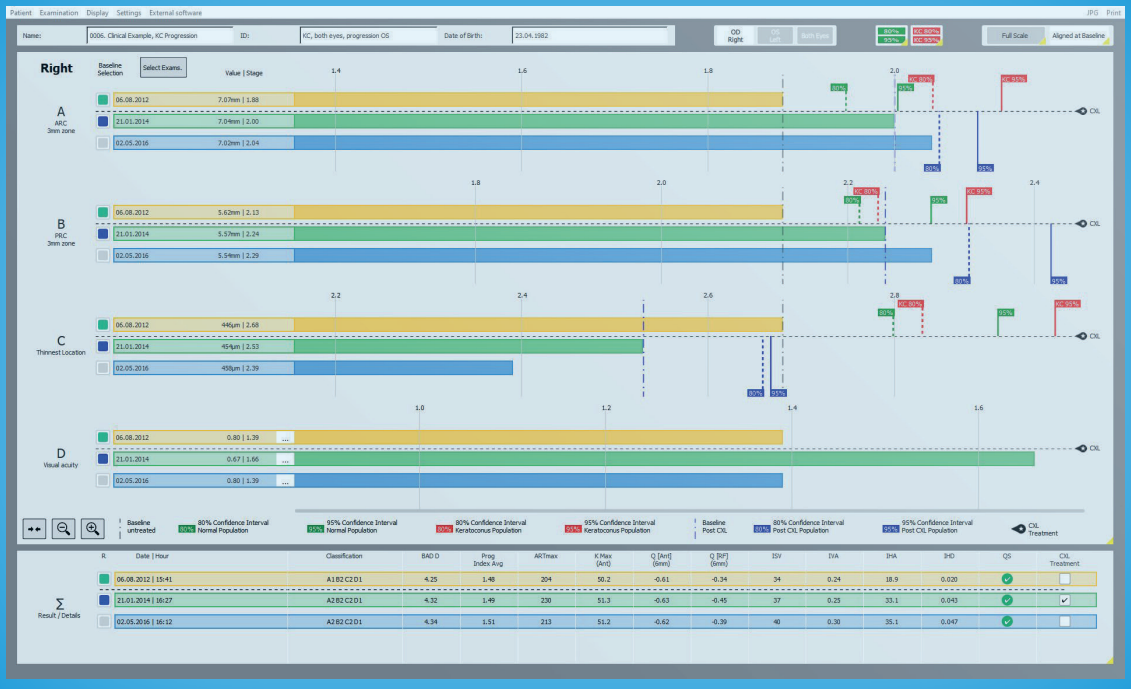

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kind of macular pathology—anything on that central visual axis," Dr. Wiley says.

"We do show patients pinhole optics with a pinhole occluder in the lane," he continues. "It's interesting, when the occluder drops in, they'll say, 'I'm seeing distance and some near vision. This is great.' Those are patients where you might be more encouraged to use it, but some patients say, 'Wait a minute, it's much more dim, you've turned the lights down. I don't like this.' We do counsel patients that this lens is going to allow less light in, but the light that does get into the eye will be more clear. There's a tradeoff and some patients appreciate that or some patients don't, so it's a good idea to show them what it's like when in the lane and rule out anybody that might have an issue with it after surgery."

Make sure to check how the patient dilates, advises Dr. Hovanesian. "You want to be able to dilate the pupil to look at the retina in the future," he says. "Make sure that you've got a patient who dilates to 6 mm or more because the outside diameter of the mask is about 3.5 mm and if they only dilate to a 4 mm pupil, it's going to be pretty hard to ever look at the retina."

Preop OCT is proving to be a helpful technology, he continues. "Any of these lenses depends upon a healthy macula," says Dr. Hovanesian. "With any of the advanced lenses, there's some forgiveness of very mild maculopathy, but we do an OCT on everybody because it's surprising the number of patients who have epiretinal membranes that aren't visible by slit lamp, especially when you're looking through a cataract. We think OCT is important for challenging patients or patients who are choosing a refractive lens."

When it comes to targeting the Apthera, Dr. Wiley advises to lean toward an intermediate vision. "When we do a pinhole aperture in the lane, somebody could be at -1 but when you drop the pinhole in they now have better distance vision," he says. "With small-aperture optics, the defocus curves work on both sides of that resting refraction so it can help give a -1 vision better distance, but also better near vision. So if you start at plano you're losing some of the depth of focus on the back side of that defocus curve. But if you target -1 or -1.25, you're maximizing the near vision and also gaining a little bit of distance vision on top of that -1 refraction."

This might differ for those with keratoconus. "There's been some discussion that because someone with keratoconus has a multifocal cornea, they can look through multiple points in that cornea," Dr. Wiley says. "We've noticed that the Apthera forces them to look through a very central part of their visual axis and sometimes that portion of the cornea may be flatter than where they're used to. That might suggest we have to target even more minus than we think. They're losing some myopia based on where they're forced to look."

For the diurnal fluctuations in patients with RK, Dr. Hovanesian says it's good to aim somewhere in the middle of the refractive range they experience. "If the cornea varies between a 42 and a 44, then you might aim for treating it as though the keratometry is 43 and they'll end up with better acuity throughout the day," he says. "Or aim for the flatter of the two options. Aim for the 42 and then during the part of the day when their cornea ends up being steeper, they'll end up with better uncorrected near vision."

• ***Implantation techniques***. "One unique thing about implantation of the Apthera is that it requires a 3.2-mm incision, which is a little larger than most of our lenses that go through a 2.4-mm or even a 2.2-mm incision instead, so that requires an extra step," says Dr. Hovanesian.

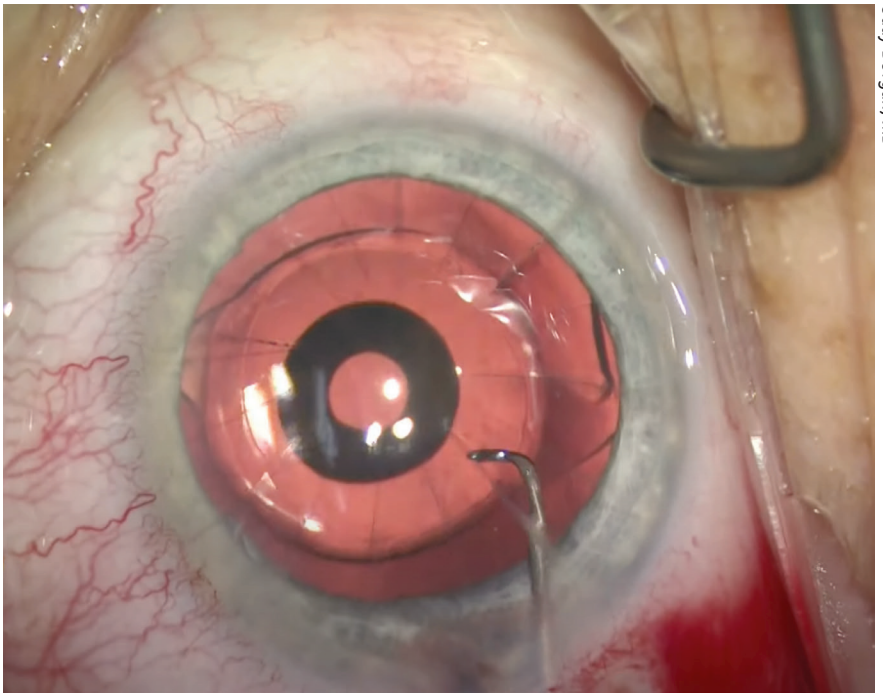
Dr. Wiley says to make sure that the lens is well-centered. "It's a stiffer lens so it's going to center itself within the bag, but if you had any kind of pathology that might allow it to decenter, that could pose an issue. You want to make sure the bag itself is normal," he says.

As mentioned earlier, the patient's ability to dilate is important. The Apthera is contraindicated for patients with a dilated pupil size less than 7 mm. "They don't want you implanting it in a small pupil because if you have to do a YAG laser you might not be able to go around the Apthera," notes Dr. Wiley. "There are mandatory online courses that surgeons have to do to make sure they understand how to do that technical component of the YAG laser."

"Just like any implant, patients can develop posterior capsular opacity," warns Dr. Hovanesian. "It's important that we YAG these the right way. What we don't want to do is YAG through the mask, because you'll cause damage to the lens and it will absorb the YAG energy and cause delamination of the lens. Damage to the mask seems to be generally well-tolerated, just like pitting of the optic when the YAG laser hits the posterior surface of any lens, but nonetheless it's damage we hope to avoid. When you're doing a YAG you often need to dilate the pupil somewhat widely and you YAG in an inverted U pattern so that you create a flap of the posterior capsule and it will tend to fall backward and remain attached at the bottom 6 o'clock position. Sometimes it's necessary to YAG through the aperture in the middle of the lens, but do that cautiously."

• ***Refractive misses***. Surgeons who are experienced with the Apthera say that refractive misses are uncommon, but there are options if it happens.

"I suppose it's more forgiving, in particular on astigmatism," says Dr. Wiley. "It can correct up to 1.5 D of astigmatism just by the aperture effect. If you have a patient you're not sure exactly where the visual axis is, the Apthera can be a little more forgiving as far as correcting some of the astigmatism, but can be more for-



Udayl Devgan, MD

Surgeons say they commonly use the Apthera IOL off-label in patients with keratoconus or previous radial keratotomy.

giving on a refractive miss. The FDA study did indicate that. However, the only downside is some of the eyes we're doing it on now are more challenging to hit the target."

Dr. Hovanesian says he favors surface ablation for refractive misses with IOLs. "However, our accuracy goes down for patients who've had prior kerato-refractive surgery because we know that epithelial remodeling in the cornea can have unexpected results," he says. "So, I sort of lean toward PRK, but with caution. We don't have a ton of those with Apthera because the lens is forgiving and because, frankly, going into this, we set the expectation with patients who have irregular corneas. We're not really doing this as a refractive procedure—we're doing it to improve their acuity, we're doing it to try to avoid a corneal transplant, to avoid a scleral contact lens in the future. But the lens is limited. Technology isn't perfect. They have to temper their anticipated results."

"It's a great lens, but like any of the presbyopic lenses there are pluses and minuses to using it," Dr. Wiley summarizes. "Some patients might notice glare or halo with nighttime activities, which seems to be on par with what we've seen with other presbyopic lenses." In the FDA study,[1] the most common visual disturbances at 12 months in the Apthera group with severe ratings were starbursts (3.6 percent), halos (3.6 percent) and glare (3 percent). Of all visual symptoms, including blurred and hazy vision, over 80 percent of subjects reported 'never experienced', 'experienced symptom but not bothered at all' or 'a little bothered' at 12 months in both the Apthera IOL and control groups, according to the study.

EVO+ ICL

The second generation of the Visian implantable collamer lens, the EVO/EVO+ Visian ICL was FDA approved in 2022. The phakic lens is approved for high myopes ranging from -3 to -20 D, with the ability to correct from 1 to 4 D of astigmatism.

"EVO is intended for the treatment of myopia and myopic astigmatism, specifically for patients who are looking for a refractive outcome and don't have cataracts," says Dr. Vukich. "It's absolutely an improvement in the ICL line. EVO simplifies the treatment since they don't need laser iridotomies, and it makes the surgery easier for the patient. The EVO ICL tends to be even more forgiving regarding the postoperative amount of vault. This is reassuring from a surgeon standpoint."

ICL technology is well-known, and advancements are bringing it to the level of LASIK correction, speculates Dr. Vukich. "It's been around for more than 20 years and it continues to gain market share," he says. "It's a very popular option in Asia where there's a higher prevalence of myopia. But within the United States now, we see a progressive increase in using the EVO in what would be considered to be the LASIK range. The EVO goes down to -3 D, the lowest power available, and we're seeing an increased uptake in the -3 to -6 D diopter range, which used to be the exclusive territory of LASIK. The continued increase in uptake for the ICL has obvious reasons: it's removable, the quality of the optics is very high, and it provides stable rehabilitation."

In the past, Dr. Wiley says he typically only used the ICL for extreme cases, but now trusts it in more routine refractive cases as an alternative to LASIK, SMILE or PRK. "In particular, we've made an effort in our practice to try to minimize offering PRK," he says. "We offered PRK for thinner corneas, dry-eye patients or patients who were worried about operating on a problematic corneal surface. Granted, PRK has those safety profiles that would make it safer than LASIK as far as ectasia or dryness, but we also found that it's just not a practice-builder. It takes a few weeks to get the best vision. Patients don't have that immediate wow effect, so it's sort of an anticlimactic experience to say the least for the patients. Now, any patient that we may have offered PRK we try to encourage the ICL, which has the

same or even better wow effect that we see with LASIK or SMILE."

Dr. Wiley continues, "We used to have a -9 or -10 cut off for ICL and we'd do LASIK or SMILE all the way up to those ranges, but now we've dropped our threshold and are trying to offer ICL as mandatory above a -6.50 or so. As much as you can do LASIK on a -6.50 or -7 patient, they do well, but their enhancement rates are a little higher, they have a little higher chance of having glare, halo or abnormal side effects. With the ICL we just don't see those. We're trying to encourage the ICL more and more for anybody in the range of ICL approval, but mandatory in patients who were considering PRK or patients in the higher-to-moderate range of myopia."

• ***Candidate selection***. As with earlier iterations of the lens, anterior chamber depth is an important factor in patient selection.

"The number one reason why we wouldn't use an ICL would be related to anterior chamber depth," says Dr. Vukich. "The FDA requires 3 mm of true anterior chamber depth, from corneal endothelium to epithelium of the lens. The EVO lens does occupy space so you need an appropriate amount of it.

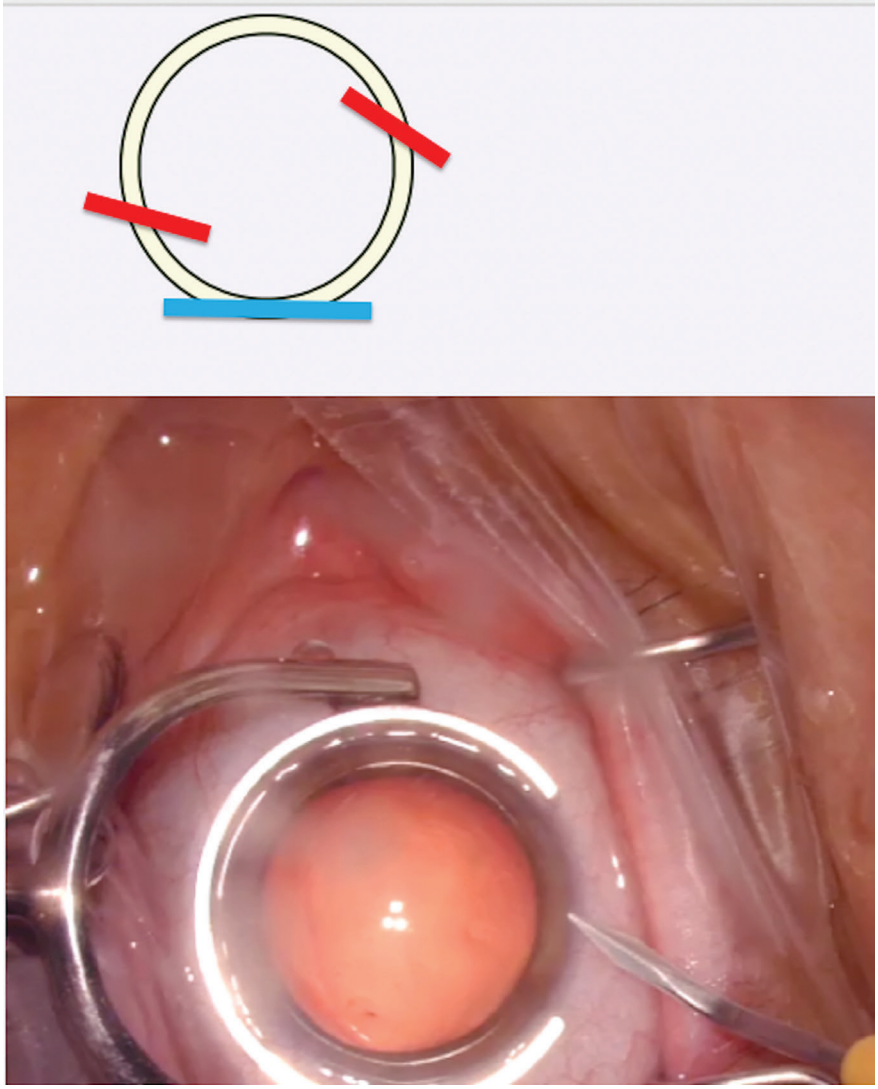
"We'd also avoid using this in anyone with a preexisting cataract," he continues. "It's proven to be a very safe lens. We implant this routinely in patients who have other conditions. For instance, if someone has elevated pressure/glaucoma, that isn't a contraindication. It's not a multifocal, so if someone is presbyopic, they'll still need to have reading glasses as is the case with any refractive procedure."

The EVO is ideal for patients with superior vision demands who also want to avoid corneal resurfacing. "I have a lot of engineer-type patients who are very particular about their vision," says Deepinder Dhaliwal, MD, who is a professor of ophthalmology and the chief of refractive surgery at the University of Pittsburgh Medical Center. "They're interested in very high-quality optics, and the EVO ICL can meet or exceed their expectations because the cornea is untouched and because of that, the quality of vision is phenomenal."

It can also be an option for patients hesitant to undergo LASIK for whatever reason. "When they realize that EVO is an additive technology, and we're not removing corneal tissue or cutting across corneal nerves, it's really kind of exciting to them, and comforting to them, too." says Dr. Dhaliwal. "Don't get me wrong, custom LASIK results are also phenomenal, but initially there's dryness, and some glare and halo. The fact that it's removeable is seen as a benefit by many patients."

• ***Preop considerations***. One of the advantages of the ICL is that it's based purely on the refractive error, says Dr. Vukich.

"You don't need to have an axial length, you don't need to have a careful assessment of the topography," he says. "We're not looking at changing the shape of the cornea like you would a corneal refractive procedure. If you can refract the patient to a given level of acuity, you can then use that same refractive power on an ICL



Deepinder Dhaliwal, MD

One of the surgical pearls for implanting the EVO ICL, offered by Deepinder Dhaliwal, MD, is to create the first paracentesis at an angle toward where the footplates will be tucked, which makes the surgery go more smoothly.

and fully expect to achieve the same level. We'll get keratometry, we'll get topographies and we'll look at the surface of the cornea as it relates to dryness or surface quality because all of those things will influence the quality of vision, but the actual refraction itself is what drives the selection of power."

Dr. Dhaliwal says it's important to follow a system when performing any refractive surgery, including EVO. "Before the actual surgery, you have to pick the ICL and there's nuances there," she says. "The power is really easy. There's an online calculator that you use, and there are four sizes. We're using OCT with the Anterion device to get certain measurements and using the LASSO formula to help us, but also, just looking at white-to-white in different ways. The white-to-white value built into the calculator was from the Orbscan. If the white-to-white that you input isn't from an Orbscan device, then you're likely going to have to make a modification to the size of the lens. Sizing is not a scary thing. It's totally doable, and Staar Surgical will help surgeons pick the appropriate size of the ICL if a surgeon has questions."

Properly sizing the ICL is an integral part of the process, adds Dr. Wiley. "We've been a big fan of using multiple sizing methods, looking at IOLMaster, Pentacam and using a handheld digital caliper for manual white-to-white," he says. "There's some great software available, in particular, Roger Zaldivar, MD, has software called the ICL Guru that uses ultrasound measurements. It seems like that's going to really be a more precise method for sizing."

EVO's central port has made it more flexible when it comes to the vault, as well. "It's made it less concerning to have a smaller vault now that we know that we're getting good aqueous flow around the lens," says Dr. Wiley. "In the past, we might have been erring a little bit on a larger vault size or larger ICL size. But now, if there's a toss up between the higher or lower vault lens, we'll go with a lower vault lens knowing that the central port allows good aqueous flow. We just don't have this concern as we did in the past for low vault sizing, such as cataract formation. Our European colleagues have informed us that the risk of cataracts with EVO is much lower than it was with traditional ICL so that's made us all feel more comfortable with lower vaulting lenses. That's given us a margin of error and safety that's made it more forgiving."

Implanting the EVO

"The lens is designed and sized to go from 3 to 9 o'clock; it always goes in the horizontal meridian," Dr. Vukich says. "Unlike an IOL, which is rotated to the axis of the astigmatism you need to correct, the ICL always goes in at 3 to 9. Now, there can be a slight clockwise or counterclockwise bias that would go with the lens that you'd use to correct—you can't have 180 different implant powers. It's plus or minus 21 degrees clockwise or counterclockwise, but essentially it's in the horizontal meridian."

It requires a 2.8-mm incision, he continues. "The surgery itself is absolutely within the skill set of any trained anterior segment surgeon. It's essentially a cataract incision without having to do the additional steps of removing a cataract once you're inside, with the lens simply injected through the incision into the anterior chamber and then positioned posterior to the iris," says Dr. Vukich.

"EVO is an easier procedure," states Dr. Wiley. "It eliminates the YAG peripheral iridotomy and those workflow concerns that made that extra step more costly, time-consuming, and annoying for the patient and the team. It's also much safer with the port."

For the best results from the EVO, Dr. Dhaliwal offers the following pearls:

• ***Dilation***. Make sure your patients are really well-dilated because it makes the surgery a lot easier.

• ***Paracentesis.*** "My first paracentesis is angled towards where the footplates are going to be tucked," she says. "For example, if I'm operating on a right eye, then my first paracentesis is more at 5:30 and it's angled nasally so that when I insert the Batlle ICL manipulator in the anterior chamber to tuck the footplate, it's easy because I'm already in the same direction where I'm going to tuck the footplate. My instrument isn't causing any corneal striae and it's a little closer to those footplates so I don't have to go all the way across the anterior chamber. This has been unbelievably helpful for me.

"After creating the first paracentesis, we instill Shugarcaine, followed by OcuCoat," Dr. Dhaliwal continues. "Then we make our second paracentesis angled toward the main incision. We create our main incision and then gently insert and unfold the ICL (which has been loaded in the injector before the procedure is started). It's elegant in its simplicity."

• ***Leave room for the ICL to unfold.*** The anterior chamber should be about 70 percent full of OcuCoat so that there's room for the ICL to unfold. Too much viscoelastic is a common mistake. Dr. Dhaliwal says she burps the incision to make sure that the anterior chamber has space for an easy unfolding of the ICL.

• ***Retract, depress and slide.*** During insertion, monitor that the leading right footplate has the orientation dot. "I'm very slow and methodical as I'm inserting the ICL to ensure the ICL is in the correct orientation," she says. "Continue to depress the plunger until the ICL has fully unfolded. The orientation dots should be on the leading right and trailing left footplates. After that, we tuck the footplates. We place OcuCoat on top of the ICL after inserting to help it settle down closer to the iris. Then we use the Batlle manipulator to just tuck the footplates under the iris. We contact the ICL in the periphery at the footplate/optic junction and retract, depress and slide it underneath

the iris.

"Another thing that's helpful is to use the manipulator in between the footplates in the periphery of the ICL to rotate it to get the footplate closer to facilitate tucking," continues Dr. Dhaliwal. "When I first started, I was scared to rotate the ICL. I would just try to get my manipulator to the footplate, wherever it was, but that was challenging because it could be an awkward position. Now I rotate the footplate closer to my manipulator, so it's much easier. There's a 'no-fly zone' in the optic—never touch the optic."

• ***Be delicate.*** Be mindful that this is a phakic eye. "If you're a very gentle cataract surgeon, you'll be an excellent EVO ICL surgeon," she says. "That's the bottom line. If you have a gentle technique and you respect the anatomy and the structures, then you can do the EVO ICL very easily. If you're a heavy-handed surgeon pushing on the eye, then you'll need to modify your technique for EVO. It's very different from a cataract lens implant where you don't have to be as gentle. You have to switch gears."

• ***Remove the viscoelastic.*** Dr. Dhaliwal says she uses a lot of irrigation when removing the OcuCoat. "I use BSS in a 5cc syringe with a hydrodissection cannula until I don't see any more movement of the OcuCoat," she says. "Then I use bimanual I/A. I do both. And because my paracenteses are a little bigger than for cataract surgery—closer to 1.5 mm—fluid can exit there. I want the viscoelastic to come out through all incisions."

• ***No miochol at the end of the case.*** Dr. Dhaliwal says she doesn't use miochol at the end of the case because she wants to keep the pupil dilated in case there's a little residual viscoelastic behind the ICL. "I also don't like to constrict the pupil in high myopes," she explains. "There's a risk of RD, and I don't want my patients to have a headache. We want their experience to be as pleasant as it can be. I always check their intraocular pressure an hour or two after surgery before they leave."

Postop Considerations

Once a patient has undergone EVO implantation, keep the following in mind:

• ***Side effects and recovery expectations.*** Patients can be fully corrected within hours after the procedure. "Unlike LASIK, in which there's pretty significant re-contouring of the cornea that occurs, and unlike a cataract operation where there's a fair amount of manipulation because of the amount of time the instrument is in the eye, the ICL is a small incision, but that incision is only used for the injection of the implant," Dr. Vukich says. "There's minimal edema and you don't see swelling of the cornea because it's a very gentle procedure. Usually by the next day we'll see patients already at their best potential acuity."

Glare was initially a worry for Dr. Dhaliwal. "I thought I'd have more patients complaining about the glare around the central port in the EVO ICL," she says. "When I switched from the Visian, which doesn't have a central opening in the optic, to the EVO ICL, which actually has five openings, I was a little worried patients would be affected by the glare after surgery. But after one month, patients typically say they don't notice it anymore. There is quick neuroadaptation to the central port.

"The other beautiful thing is that we don't have to do iridotomies anymore, so only one surgery is required," continues Dr. Dhaliwal. "And the recovery is a little faster than my LASIK patients because there's no corneal flap that has to heal. I'm not worried about DLK or dryness and the ICL is very biocompatible. Our patients use steroids for two weeks: four times a day for one week, and then twice a day for another week and that's it. When I look at these eyes after surgery, they're quiet."

• ***Counseling patients as their vision changes***. Patients who are receiving the EVO ICL are pre-presbyopic, and the day will come when their vision changes naturally due to age and/or cataract development.

Dr. Dhaliwal notes that EVO patients can be candidates for any IOL technology down the road that they want since their corneal optics are unchanged. "We know that moderate to high myopes will develop cataracts at an earlier age," she says. "They're happy to learn that having EVO ICL surgery won't burn any bridges for future technology. Also, unlike post-corneal refractive surgery, there are no special formulae that need to be employed when selecting an IOL. Biometers can easily measure through the ICL."

Dr. Vukich counsels patients that the EVO doesn't stop the hands of time. "I tell my patients who are 20- or 21-years-old, 'Look, you're going to get gray hair and wrinkles someday, too.' They laugh but the reality is, there's a natural order and progression of changes and the EVO just sets the refractive error back to zero," he says. "Of course, when they hit age 45 their vision will be different. There really isn't a solution for presbyopia at this point, so they'll need to wear reading glasses—that's the solution. Who knows, maybe by the time these 20-year-olds are in their 40s there will be a better solution."

Ultimately, the EVO continues to gain traction in the market, due in part to its accessibility. "It's within the skill set of any trained anterior segment surgeon," concludes Dr. Vukich. "You don't need an excimer laser or a femtosecond laser. You don't need all of the infrastructure that's associated with LASIK. What you have is essentially something that can provide a positive service for patients by giving them an emmetropic result." ◀

1. Hydrophobic Acrylic Small Aperture Intraocular Lens Directions for Use. https://www.accessdata.fda.gov/cdrh_docs/pdf21/P210005C.pdf. Accessed April 2, 2024.

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WHAT'S ON THE HORIZON FOR KERATOCONUS

The number of keratoconus treatment options is growing, with new techniques and devices in development.

ANDREW BEERS
ASSOCIATE EDITOR

Various studies have suggested that the incidence rate of keratoconus is between 0.2 and 4,760 per 100,000 people and 1.5 and 25 per 100,000 people/year.[1] Previous treatment options for the masses included cornea transplant, penetrating keratoplasty, Intacs and various types of lenses—rigid gas permeable lenses, scleral lenses and soft contact lenses for milder cases. But what if every keratoconus patient had a host of novel treatment options available to them?

Corneal collagen cross-linking has been the cutting-edge treatment option for keratoconus,[2] and a number of ophthalmic medical technology and pharmaceutical companies have been pioneering the latest advancements in corneal cross-linking, and, in some cases, researchers have been developing management techniques in tandem with this technology. To appreciate the scope of the developments in keratoconus management, here's a list of devices and techniques that may eventually come to your practice.

CXLens (TECLens)

TECLens announced its pilot trial results for its transepithelial corneal crosslinking contact lens device, CXLens, in 2021. Now, the company is gearing up for Phase II/III of U.S. Food and Drug Administration trials.

CXLens is an on-eye UV-A light-emitting contact lens device that operates using fiber optics for corneal cross-linking. Its main use is for the treatment of keratoconus, but Roy S. Chuck, MD, the Chairman of Ophthalmology at Albert Einstein College of Medicine and cofounder of TECLens, notes that the device is beginning to be applied for treating refractive errors.

"The original pilot trial publication of the CXLens described that the device was putting the UV light source on a controlled contact lens," Dr. Chuck explains. "Since then, we've added a feedback element. This is an ultrasound biosensor in the lens. So, in real time, you can cross-link, and you can go ahead and monitor the cross-link and really monitor the cornea as it stiffens." The idea for this additional technology was to provide surgeons with ample control while performing the cross-linking procedure. To further strengthen the con-

TECLens

TECLens' partnership with SERVImed will allow for the incorporation of Ribocross with CXLens treatment. The riboflavin solution is maintained in a scleral lens reservoir.

This article has no commercial sponsorship.

Dr. Chuck is the cofounder of TECLens. **Dr. Jacob** has no financial interests to disclose.

trol of the procedure, TECLens has developed more advanced features.

"We're also starting to develop more computer modeling to go ahead and use in conjunction with the cross-linking and ultrasound biosensors," Dr. Chuck continues. "The ultimate goal is control. If you can control shape change and stiffening change in the cornea using these three elements of cross-linking, feedback of ultrasound and computer modeling to help guide the whole thing, you should have something that's quite precise and hopefully can control the cornea and it's reshaping in all kinds of ways."

In addition to these novel approaches to development, TECLens has partnered with SERVImed Industrial Spa to combine their product Ribocross (riboflavin 0.1%; dextran 10%; Vitamin E TPGS solution) with CXLens technology. Although Ribocross has received Orphan Drug Status from the FDA, Dr. Chuck explains that this solution won't be introduced with CXLens until the device is fully developed and approved.

According to the pilot study,[3] nine corneal transplant candidates with advanced keratoconus received a scleral lens reservoir. The lenses were fixed with 0.007% benzalkonium chloride preserved with 0.25% riboflavin-monophosphate. After 30 minutes, the lens was removed, and subjects received treatment from the CXLens (375-nm UV-A light at 4mW/cm^2). After another 30 minutes, each subject had received a dose of 7.2 J/cm^2. During the follow-up after six months, subjects who were treated with the CXLens had an average -1.0 ±1.6 D decrease in maximum keratometry.

"Our goal has always been to address the issue of precision medicine, patient specific medicine and customized control," says Dr. Chuck. "As we go forward, it's all about treating the patient using their own data rather than trying to guess, and we're trying to take the guesswork out of what we do by doing everything with ultrasound monitoring and finite element modeling. Hopefully, this will give us the most precise correction possible."

TECLens

The CXLens platform includes a compact system with lenses that emit UV-A light rays for cross-linking treatment. Two lenses are attached to the device to perform cross-linking on both eyes simultaneously.

Glaukos

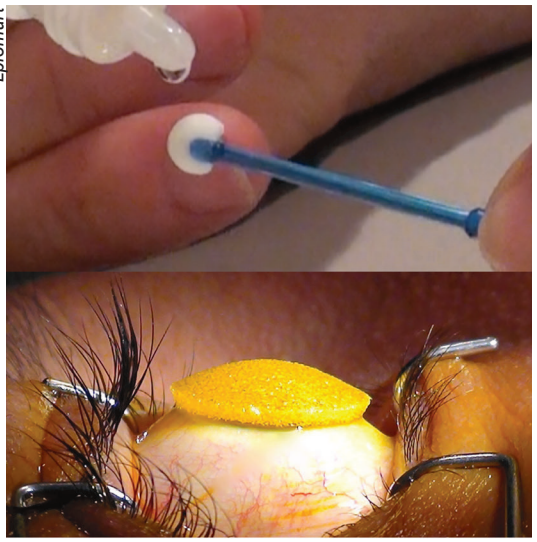
Glaukos was the first company to have an FDA-approved corneal cross-linking device. Their latest FDA approved epithelium-off riboflavin solution, Photrexa, is used along with Glaukos' iLink Corneal Cross-Linking system. Currently, Glaukos is developing their epithelium-on platform, Epioxa, and a third-generation corneal cross-linking system.

• ***Epioxa***. In 2023, Glaukos announced that the Phase III FDA trial for Epoxia had reached enrollment completion. This confirmatory pivotal trial has enrolled 312 eyes for epi-on corneal cross-linking treatment. The subjects will be randomly selected in a 2:1 ratio to receive Epioxa therapy or a placebo. This trial will evaluate whether the therapy is safe and effective when attempting to stop the progression of keratoconus and/or reduce the maximum corneal curvature (Kmax) for keratoconic eyes. In a press release, Glaukos stated that the primary endpoint that needed to be achieved was the mean change in Kmax from baseline through a 12-month follow-up period. If there's a significant difference between the treated subjects and the control's primary endpoint results and if there's a ≥1 D difference, then the study would be considered a success by the FDA.

• ***NXL UV-A Device (Third Generation).*** Additionally, Glaukos reported its findings on the safety of its third-generation corneal cross-linking system with various riboflavin doses.[4] The company reported that three subjects received a high dose of UV-A while nine subjects received low, medium or high doses of UV-A in a dose-escalating manner. Every patient received epi-on therapy for this study. In 2023, only a total of 17 percent of subjects completed the six-month follow-up period and showed mild adverse events similar to those observed in conventional cross-linking treatments. At ASCRS 2024, Glaukos reported the 12-month data from the study, and they noted no change in adverse events from the six-month follow-up.

• ***IVMED-80.*** After Glaukos entered a licensing agreement with

EpiSmart



EpiSmart's EpiPrep disposable wand (Top) and disposable loading sponge (Bottom).

iVeena to develop and commercialize IVMED-80 (copper sulfate eye drops), the pharmacological treatment is currently undergoing Phase III FDA trials. In 2020, under the leadership of iVeena, a team of researchers evaluated the safety and preliminary efficacy of the eye drops in Phase I/IIa FDA trials.[5]

IVMED-80 was developed to increase lysyl oxidase, a cross-linking enzyme that, when decreased, is linked to keratoconus.[6] During the 26-week trial, a total of 36 patients were randomly divided equally into three treatment groups: Group 1 received IVMED-80 treatment for six weeks, then stopped treatment for the remaining 20 weeks, Group 2 received IVMED-80 treatment for 16 weeks, then stopped treatment for the remaining 10 weeks, and Group 3 received placebo eye drops for 16 weeks, then stopped treatment for the remaining 10 weeks.

According to the study, no adverse events were reported during the 16 weeks of treatment. At 16 weeks, 19 IVMED-80 patients showed a 1-D reduction of Kmax, while the placebo group progressed by 0.46 D of Kmax. Subjects in Group 1 showed a 0.46 D reduction of Kmax at two months, but their eyes reverted back to baseline by 16 weeks. The researchers reported that there was no clinically significant effect on IOP or other ocular findings.

EpiSmart (Epion Therapeutics)

According to their website, Phase III FDA trials (Apricity A and Apricity B) for Epion's minimally invasive keratoconus treatment, EpiSmart, commenced in 2023. They plan on enrolling 800 subjects from across the United States, including patients as young as 8 years old, as long as they've met the enrollment criteria.

This epi-on platform includes RiboStat, a high concentrated riboflavin/sodium iodide solution. This is administered using EpiPrep, a two-part system including a disposable wand to enhance epithelial permeability and a disposable loading sponge to sustain high drug concentration during stromal loading. This is when the EpiSmart UV-A device is introduced to perform epi-on corneal cross-linking.

During Phase II FDA trials,[7] Epion researchers enrolled 2,228 subjects who were assessed at six and 12 months postoperatively. The subjects were randomly divided into three different treatment groups, each receiving various doses of UV-A treatment. The doses administered were 2.4 J/cm^2 over 20 minutes, 3.6 J/cm^2 over 20 minutes and 3.6 J/cm^2 over 30 minutes. The primary endpoint observed by the researchers was logMAR CDVA, while secondary endpoints included logMAR UCVA, Kmax and minimum corneal thickness.

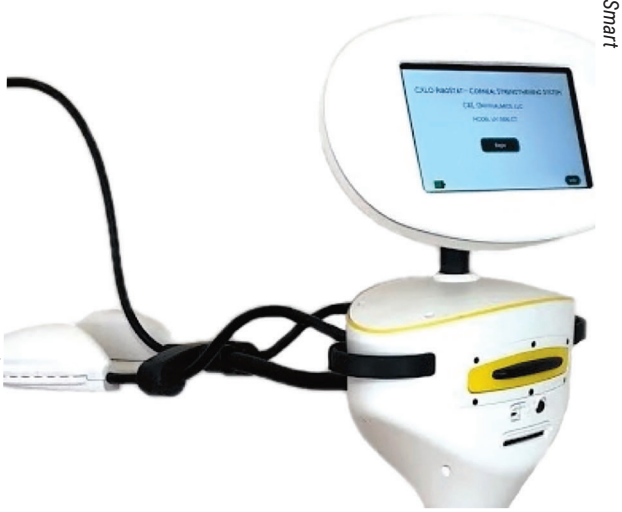
Researchers reported that 1,922 subjects were diagnosed with keratoconus and the other subjects had postsurgical or other ectasias. The primary endpoint was achieved and resulted in a significant improvement in CDVA for all groups. UCVA and Kmax secondary endpoints were significant as well, but minimum corneal thickness remained unchanged. Although no serious adverse events were reported, 195 cases (8.7 percent) had at least one adverse event. The most prevalent complication was a mild corneal epithelial defect, which was found in 31 cases (1.4 percent).

Omni CXL (Micro Medical Devices)

According to Micro Medical Devices, the Omni CXL is a transportable corneal cross-linking system awaiting market approval in the U.S. This device received it's CE mark in 2006 for European distribution and now it's in clinical use in over 100 countries.

Micro Medical Devices explains that the device can be tuned to output energy from 3 mW to 45 mW per cm^2 with automatic time adjustment. The system is built with an integrated infrared camera for eye tracking to ensure proper distance. Both the tracking area and the threshold can be individually set. Automatic riboflavin selection recommendation is available when using the integrated pachymeter. Addition-

EpiSmart



EpiSmart's corneal collagen cross-linking system uses an epi-on approach.

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EYLEA HD for Wet AMD, DME, and DR

An interactive look at PULSAR and PHOTON, the pivotal clinical trials supporting the FDA approval of EYLEA HD. Content will also cover patient cases where EYLEA HD was considered as a treatment option.

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Palisade
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Registration: 6:30 PM PT
Dinner/Reception: 7:00 PM PT

Presenter
David Almeida, MD, MBA, PhD
Vitreoretinal Surgeon
Erie Retinal Surgery
Erie, Pennsylvania

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- EYLEA HD 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 HD.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis and retinal detachments and, more rarely, retinal vasculitis with or without occlusion. Proper aseptic injection technique must always be used when administering EYLEA HD. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment, or retinal vasculitis without delay and should be managed appropriately.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA HD. 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 HD. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in the wet AMD study (PULSAR) from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with EYLEA HD compared with 1.5% (5 out of 336) in patients treated with EYLEA 2 mg. The incidence in the DME study (PHOTON) from baseline to week 48 was 3.1% (15 out of 491) in the combined group of patients treated with EYLEA HD compared with 3.6% (6 out of 167) in patients treated with EYLEA 2 mg.

ADVERSE REACTIONS

- The most common adverse reactions (≥3%) reported in patients receiving EYLEA HD were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA HD and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

- EYLEA® HD (aflibercept) Injection 8 mg is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

Please see accompanying for full Prescribing Information for EYLEA HD.

DME = Diabetic Macular Edema, DR = Diabetic Retinopathy, FDA = Food and Drug Administration, Wet AMD = Wet Age-related Macular Degeneration

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
EYLEA HD is indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis, Retinal Detachments, and Retinal Vasculitis with or without Occlusion
Intravitreal injections including those with aflibercept have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*] and, more rarely, retinal vasculitis with or without occlusion [*see Adverse Reactions (6.2)*]. Proper aseptic injection technique must always be used when administering EYLEA HD. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment or retinal vasculitis without delay and should be managed appropriately [*see Dosage and Administration (2.6) in the full Prescribing Information and 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 HD [*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 [*see Dosage and Administration (2.6) in the full Prescribing Information*].

5.3 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA HD. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in the wet AMD study (PULSAR) from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with EYLEA HD compared with 1.5% (5 out of 336) in patients treated with EYLEA 2 mg. The incidence of reported thromboembolic events in the DME study (PHOTON) from baseline to week 48 was 3.1% (15 out of 491) in the combined group of patients treated with EYLEA HD compared with 3.6% (6 out of 167) in patients treated with EYLEA 2 mg.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis, Retinal Detachments and Retinal Vasculitis with or without Occlusion [*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 1164 patients were treated with EYLEA HD and 503 patients were treated with EYLEA 2 mg in two clinical studies. The most common adverse reactions reported in ≥3% of patients treated with EYLEA HD were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage. The data described below reflect exposure to EYLEA HD or EYLEA 2 mg in controlled clinical studies (PULSAR and PHOTON), each for 48 weeks *[see Clinical Studies (14.1, 14.2) in the full Prescribing Information]*.

Table 1: Adverse Reactions (≥1%) in at least one group in the PULSAR or PHOTON studies

	PULSAR			PHOTON		
Adverse Reactions	EYLEA HD q12 (n=335)	EYLEA HD q16 (n=338)	EYLEA 2q8 (n=336)	EYLEA HD q12 (n=328)	EYLEA HD q16 (n=163)	EYLEA 2q8 (n=167)
Cataract[a]	4%	4%	4%	3%	6%	3%
Conjunctival hemorrhage[a]	3%	2%	1%	4%	4%	4%
Intraocular pressure increased[a]	4%	4%	2%	3%	1%	4%
Ocular discomfort/eye pain/eye irritation[a]	3%	3%	2%	4%	2%	4%
Vision blurred[a]	4%	6%	7%	3%	3%	4%
Vitreous floaters[a]	1%	4%	3%	5%	2%	3%
Vitreous detachment[a]	2%	3%	2%	4%	2%	1%
Corneal epithelium defect[a]	2%	2%	3%	3%	6%	1%
Retinal hemorrhage	3%	3%	4%	0%	4%	1%
Intraocular inflammation[a]	1%	1%	1%	1%	0%	1%
Retinal pigment epithelial tear/ epitheliopathy[a]	2%	1%	2%	<1%	0%	0%
Vitreous hemorrhage	<1%	1%	1%	2%	1%	1%
Retinal detachment[a]	1%	<1%	0%	<1%	1%	0%
Foreign body sensation in eyes[a]	1%	1%	2%	<1%	0%	0%
Retinal pigment epithelial detachment[a]	1%	1%	2%	0%	0%	0%

[a]Represents grouping of related terms

Adverse drug reactions (ADRs) reported in <1% of participants treated with EYLEA HD were ocular hyperemia (includes adverse events of conjunctival hyperemia, conjunctival irritation, ocular hyperemia), lacrimation increased, eyelid edema, hypersensitivity (includes adverse events of rash, urticaria, pruritus), retinal tear, and injection site hemorrhage.

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

Eye disorders: retinal vasculitis and occlusive retinal vasculitis related to intravitreal injection with aflibercept (reported at a rate of 0.6 and 0.2 per 1 million injections, respectively, based on postmarketing experience from November 2011 until November 2023).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary

Adequate and well-controlled studies with EYLEA HD 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 exposure (based on AUC for free aflibercept) was approximately 0.9-fold of the population pharmacokinetic estimated exposure in humans after an intravitreal dose of 8 mg [*see Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA HD can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1) in the full Prescribing Information*], treatment with EYLEA HD may pose a risk to human embryofetal development. EYLEA HD 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 0.9-fold of the population pharmacokinetic estimated systemic exposure (AUC) in humans after an intravitreal dose of 8 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 HD is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA HD and any potential adverse effects on the breastfed child from EYLEA HD.

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 4 months after the last intravitreal injection of EYLEA HD.

Infertility

There are no data regarding the effects of EYLEA HD on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose 91 times higher (based on AUC of free aflibercept) than the corresponding systemic level estimated based on population pharmacokinetic analysis in humans following an intravitreal dose of 8 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1) in the full Prescribing Information*].

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

8.5 Geriatric Use
In PULSAR, approximately 90% (604/673) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 51% (343/673) were 75 years of age or older.
In PHOTON, approximately 44% (214/491) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 10% (50/491) were 75 years of age or older.

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

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA HD administration, patients are at risk of developing endophthalmitis, retinal detachment, or retinal vasculitis with or without occlusion. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients and/or caregivers 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 HD and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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ally, patient data and treatment settings can be exported as a PDF and saved to the patient's medical record.

Micro Medical Devices filed for FDA market approval in 2018.

CAIRS

"Corneal allogenic intrastromal ring segments, or the CAIRS technique, was a method that started in 2015 to treat keratoconus," says Soosan Jacob, MD, the director and chief of Dr. Agarwal's Refractive and Cornea Foundation and developer of CAIRS. "CAIRS represents the use of any kind of allogenic tissue which is inserted into the cornea as segments, which could be either uniform segments or customized segments.

Micro Medical Devices

Omni CXL portable system can be stored away and transported with the compatible case. This is useful for traveling or medical mission trips the company says.

"Since about 2018, we started customizing CAIRS," continues Dr. Jacob. "This is true customization, not just based on the arc length or location, but actually based on the individual patient's keratometric maps, thickness maps and other maps. What you have to realize is that no two keratoconic patients are similar. Even if they fall into broadly the same phenotypic classes. Because we customize for every zone of the patient's map, we have variable thicknesses available with CAIRS, which gives you much better customization and therefore improved visual acuity results.

"We use a double-bladed design, which is patented, for cutting the CAIRS segments, and this gives us the ability to really exquisitely customize to each patient, or rather to each patient's type of keratoconus," says Dr. Jacob. "CAIRS is a minimally invasive surgery because the entire surgery is done through about a 1-mm incision or 1.5-mm incision and the channels are created using a femtosecond laser. So, we use the laser to create the CAIRS channel and then implant the CAIRS segments into the channels."

When it was first introduced, surgeons would make a manual incision and implant the donor tissue with SK Intacs as a guidewire.[8] Now, many studies are observing the safety and efficacy of femtosecond-assisted CAIRS procedures. At ASCRS 2024, Bianca N. Susanna, MD, reported on the latest research findings for femtosecond laser assisted personalized CAIRS implantation in keratoconic eyes.[9] After three months, subjects' UDVA improved from 0.01 ±0.06 preoperatively to 0.29 ±0.2 on the last follow-up day. Also, CDVA improved from 0.29 ±0.13 to 0.5 ±0.24. A total of 21 patients gained two or more Snellen lines of CDVA. Furthermore, spherical equivalent (-8.87 ±2.07 D to -2.90 ±4.45 D) and cylinder (-3.75 ±2.11 D to -2.35 ±0.91 D) improved for subjects. It was reported that topographic astigmatism increased from 4.20 ±2.75 to 5.03 ±2.46. During the follow-up period, no serious adverse events were observed.

After the allogenic tissues are implanted, the cornea undergoes cross-linking treatment. Dr. Jacob explains that both conventional accelerated cross-linking and accelerated contact lens-assisted cross-linking can be employed during the procedure, but each method is used for specific cases.

"When the minimum stromal thickness is less than 400 µm, we go in with CACXL, which is contact lens-assisted cross-linking," explains Dr. Jacob. "If there's more than 400 µm, we do conventional accelerated cross-linking. In both these situations, the power and the duration that we use is 10 mW/cm^2 for nine minutes."

Published in 2014, the first study on contact lens-assisted cross-linking showed the safety and effectiveness of the treatment, proponents say.[10] This treatment uses an ultraviolet barrier-free soft contact lens that's placed on the patient's cornea after being soaked in iso-osmolar riboflavin 0.1% for 30 minutes. As Dr. Jacob stated previously, the necessary corneal thickness for CACXL is less than 400 µm, and this study shows that the minimum thickness requirement for CACXL treatment is 350 µm. This method thickens the cornea to more than 400 µm, which is why it's applied when a patient is seen with a stromal thickness of less than 400 µm.

Dr. Jacob adds that CACXL has its advantages when combined with CAIRS. She explains that in some cases, the thickness of the cornea is less than the minimum thickness needed for CACXL. After implanting the allogenic tissue into the eye, the cornea thickens, allowing patients to be treated with CACXL.

"We have done this kind of approach in some cases of topographic-guided PRK where the patient

(Continued on p. 60)

HOW GOOD IS YOUR NOMOGRAM?

For improved outcomes, refractive surgeons should consider these key variables and how to incorporate shared data from others, surgeons say.

LIZ HUNTER
SENIOR EDITOR

Accuracy in refractive surgery is a paramount goal for both surgeon and patient. "As refractive surgeons, the pressure has always been on us to get an exact result," says Andrew I. Caster, MD, a refractive surgeon in Beverly Hills, California. "We've always told patients that there's some degree of variability and that a certain percentage are going to need to have a touch-up done, but the onus of keeping that touch-up number as low as possible has always been on us."

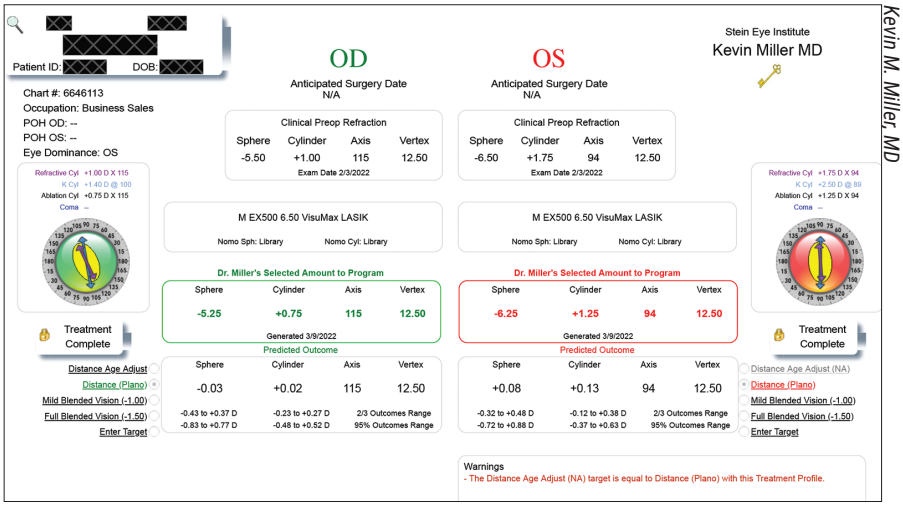
Nomograms can help better predict the outcomes of corneal-refractive surgery and can minimize the need for enhancements. These equations may be adjusted depending on various factors, including laser, patient demographics, surgeon and environment, to name a few. And although many surgeons in the early days of refractive surgery may have relied on Excel spreadsheets for their personal nomograms, they can now take advantage of nomogram software that synthesizes data from more surgeons and makes it accessible to others.

We spoke with a few refractive surgeons about the necessity of nomograms, the variables to consider when making adjustments and how shared nomograms are impacting results.

The Role of Nomograms

Commercially available laser systems take into account their own technical specifications, as well as surgical technique, operating room environment and patient demographics.[1]

"In medical procedures, calculations and processes are established to produce a desired outcome," says Kevin M. Miller, MD, of the Stein Eye Institute at the University of California Los Angeles. "However, realized outcomes often differ from desired outcomes because biological and environmental differences from person to person, site to site, and machine to machine exist.



Kevin M. Miller, MD

Shared nomogram software, such as this one from SurgiVision (enlarged to show detail), is constantly updated with data and can be personalized with different variables. Here, the software shows the surgeon the amount to program and the predicted outcome, as well as the results of the most recent eyes they operated on.

This article has no commercial sponsorship.

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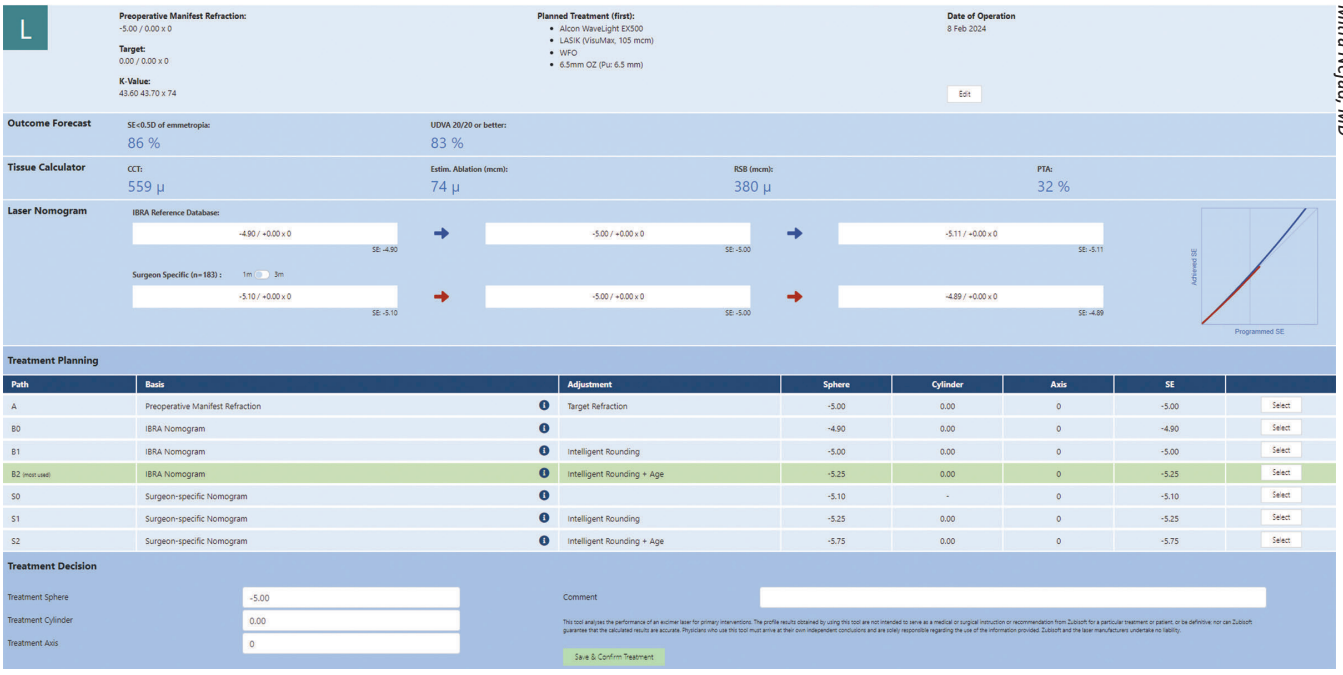


An example of the IBRA refractive nomogram software that shows the proposed treatment plan for the surgeon to program based on the nomogram chosen and the predicted outcome.

Variability in wound healing from one individual to another is an example. A nomogram considers the actual outcomes of a procedure and modifies either the inputs to the calculations and processes, or the calculations and processes themselves, in an endless feedback loop that drives the system toward the desired outcome with each iteration."

Nomograms also evolve constantly as techniques and technology change over time. "When I first started performing LASIK, which was back in 1996, I wrote my own program for nomograms, but it just did a linear analysis," recalls Dr. Caster. "Now the new programs do binomial analyses so they're more accurate."

Nomograms can't be developed without the diligent tracking of outcomes, says Lisa McIntire, MD, CEO of Speck Eye Care in Austin, Texas. "In the early days, the best surgeons—the ones who got the best outcomes and did the best work—were tracking their outcomes in an Excel spreadsheet," she says. "And I say the very best ones because not everybody did it. Not everybody tracked outcomes at all, and not everybody tracks outcomes today and that is the truth. Not everybody does it. It's the best way to get the best results, but it takes more time and it takes effort. You need to hire someone to upload data into these nomograms and use technician time to take these extra steps or maybe do it yourself. But I believe that it's of the utmost importance as we try to standardize and universally improve outcomes across our industry that we really hold ourselves accountable to these higher standards."

Dr. Miller says surgeons feed those outcomes into a nomogram and the nomogram adjusts the inputs so that the desired outputs are achieved. "Even knowing that lasers become better with each successive generation, there will always be variables that make one laser different from another laser, and outcomes with the same laser differ from one part of the world to another," he says.

Variables to Consider

There's no one right way to design a nomogram, but the more variables a surgeon includes in the equation, the more likely the outcome is to be successful.

The basis for any refractive surgery nomogram must include the variables for manifest refraction values: sphere; cylinder; and axis.

"In the case of refractive surgery (LASIK, PRK, SMILE), the primary input to a laser is the patient's refractive error," says Dr. Miller. "Surgeons enter the spherical and cylinder errors and the axis of the cylinder, and these entries constitute the primary basis for treatment. Optical zone diameter and flap or cap thickness, in the case of LASIK and SMILE, are secondary inputs. Now, if a surgeon enters the refractive error 'straight up' with no adjustment, odds are the laser he or she uses will produce a slightly different outcome than the expected one. The greater the refractive error, especially the cylinder error, the greater likelihood of an outcome error."

Most lasers will be very precise and produce the exact same output every single time they fire, he continues. "This may not be true, however, if a laser is out of calibration or the temperature and humidity in the treatment room are out of range," says Dr. Miller. "Because biological and environmental variations exist, however, even if one enters the same correction for 100 dif-

Table 1. Comparison of different nomogram proposals
From: The art of nomograms (Mosquera A, et. al[1])

Attempted			Nom 1: Sph + negCyl			Nom 2: Sph + posCyl			Nom 3: SEq + Ast			Nom 4: Cyl1 + Cyl2			Nom 5: SEq + (C+,Cx)		
Sphere (D)	Cylinder (D)	Axis (deg)	Sphere (D)	Cylinder (D)	Axis (deg)	Sphere (D)	Cylinder (D)	Axis (deg)	Sphere (D)	Cylinder (D)	Axis (deg)	Sphere (D)	Cylinder (D)	Axis (deg)	Sphere (D)	Cylinder (D)	Axis (deg)
−3.00	0.00	0	−3.25	0.02	0	−3.29	0.02	0	−3.28	0.02	0	−3.27	0.00	0	−3.26	−0.02	0
0.00	-2.00	15	−0.41	−2.05	15	−0.27	−2.04	15	−0.34	−2.04	15	−0.38	−1.93	15	−0.34	−2.03	15
−3.00	−2.00	150	−3.25	−2.04	150	−3.18	−2.03	150	−3.21	−2.03	150	−3.27	−1.92	150	−3.21	−2.02	150
−1.50	−1.00	45	-1.83	−1.01	45	-1.78	−1.01	45	-1.81	−1.01	45	-1.82	−0.96	45	-1.80	−1.02	45
−4.75	−3.25	120	−4.90	−3.31	120	−4.82	−3.30	120	−4.84	−3.31	120	−4.95	−3.11	120	−4.86	−3.26	120
4.75	-3.25	75	4.11	−3.36	75	4.43	−3.33	75	4.27	−3.35	75	4.21	−3.14	75	4.25	−3.29	75
2.00	-2.00	90	1.49	−2.05	90	1.68	−2.04	90	1.58	−2.05	90	1.55	−1.93	90	1.57	−2.03	90
3.00	6.00	165	2.44	−6.20	165	2.86	−6.14	165	2.67	−6.17	165	2.52	−5.78	165	2.62	−6.04	165

Ast = astigmatism; C + = cardinal astigmatism; C x = oblique astigmatism; deg. = degree; negCyl = negative cylinder; Nom = nomogram; SEq = spherical equivalent; Sph = sphere

A group of researchers constructed seven nomograms for eyes treated with LASIK for myopic astigmatism and found nomograms 5, 6 and 7 detected significant astigmatic differences. They concluded that their nomograms suggested minor improvements vs. actual observed outcomes.

ferent eyes with the exact same refractive error, after the treatments are done, one will observe variability in the outcomes, both in terms of accuracy and precision. So, to improve the results, the surgeon has to look at the mean resultant error, determine how much it's off, and figure out how to tweak the inputs or the treatment calculations to get the desired output."

Dr. Caster adds that nomograms can counter those situations when a laser isn't completely accurate. "For instance, with the EX500 (Alcon) that I use, the laser runs a little cold on the lower end of the myopia range and it runs a little hot on the upper range," he says.

"All lasers tend to be pretty accurate at treating low spherical errors, but at higher spherical and cylinder errors, they tend to start benefiting from nomogram adjustments," says Dr. Miller. "This is especially true of high cylinder errors."

In a retrospective analysis,[1] a group of researchers constructed seven nomograms based on the sphere, cylinder and axis of 150 consecutive eyes treated with LASIK for myopic astigmatism *(Table 1)*.

All nomograms detected subtle differences in the spherical component ($p<0.0001$). Nomograms 5 and 7 (using power vectors) and 6 (considering axis shifts) detected significant astigmatic differences (nomogram 5, $p<0.001$; nomogram 6, $p<0.05$; nomogram 7, $p<0.005$ for cardinal astigmatism, $p=0.1$ for oblique astigmatism). The researchers observed mild clinically relevant differences (~0.5 D) in sphere or astigmatism among the nomograms; differences of ~0.25 D in the proposals for sphere or cylinder weren't uncommon, and concluded that all nomograms suggested minor improvements versus actual observed outcomes.

The location of your practice also plays a role in nomograms. "Modern lasers provide excellent results in clinical trials for a wide range of refractive errors, however, surgical technique and operating environment, including ambient humidity, altitude, and other factors can affect outcomes," says Y. Ralph Chu, MD, of the Chu Vision Institute in Bloomington, Minnesota. "For LASIK and PRK, the excimer laser platform is sensitive to ambient humidity and hydration levels of the stromal bed. Being aware of where the surgical practice is located such as altitude and humidity level is important to consider when looking at a surgical nomogram.

"Whether the surgeon likes to perform an ablation on a dry stromal bed or with slight moisture on the bed is also important when evaluating a nomogram," he continues. "When using a femtosecond laser to create ablations like in the SMILE procedure, the femtosecond laser is less dependent on the ambient humidity and the environment. While monitoring outcomes is important because each laser has its own specific characteristics, environmental conditions are less of a consideration when looking at nomogram development during the SMILE procedure."

The other factor to consider when developing a nomogram is the age of the patient. "This is because healing characteristics change as patients age," says Dr. Chu. "The general consensus is that younger patients may have a slightly higher tendency toward regression of refractive effect as compared to older patients. Younger patients also tend to tolerate residual refractive error because of their accommodative ability. Older patients may prefer a

	Nom 6: Cyclotorsion			Nom 7: SEq + C+ + Cx			Max. internomogram difference		
	Sphere (D)	Cylinder (D)	Axis (deg)	Sphere (D)	Cylinder (D)	Axis (deg)	Sphere (D)	Cylinder (D)	Axis (deg)
	−3.28	0.02	0	−3.23	-0.08	98	0.06	0.09	98
	−0.35	−2.01	15	−0.39	−1.93	14	0.14	0.12	1
	−3.22	−2.00	150	−3.28	−1.88	150	0.10	0.15	0
	-1.82	−1.00	45	-1.86	−0.91	47	0.08	0.11	2
	−4.86	−3.26	120	−4.91	−3.15	118	0.13	0.20	2
	4.25	−3.30	75	4.26	−3.32	77	0.32	0.22	2
	1.57	−2.02	90	1.62	−2.12	90	0.19	0.19	0
	2.63	−6.08	165	2.58	−5.96	166	0.41	0.42	1

slight undercorrection towards myopia given the need for improved depth of focus for reading. This isn't surgeon- or laser-dependent; it's patient-specific variables that come into consideration when developing a nomogram."

Dr. McIntire says to be cognizant not to over-minus young patients. "It's easy to do because their accommodation is still intact," she says. "We can use this to our advantage a little bit when we do our procedure. The nomograms will all account for this; they will often give a slightly more minus treatment to a young person than to an older person who's lost their ability to accommodate. The reason for this is that the young person is able to accommodate so they're going to see well and automatically accommodate right through whatever is there, maybe it's -0.25 or less of residual myopia. Over time, as the epithelium starts to remodel it'll give the patient a little bit more of a long-lasting effect. We wouldn't do that in somebody who's in their 40s or presbyopic because they can't accommodate and they're not going to be happy with the answer that their epithelium is going to remodel—they just want to see.

"Also, the 40-year-old has less time to live with that treatment, because most likely in the next 15 to 20 years that person is going to have a lens replacement surgery and their refraction will be addressed by a new procedure," she continues. "Whereas, an 18-year-old might have 40 years to live with this procedure so we give them a little bit more wiggle room by adding some minus there."

Dr. Caster also adjusts for age. "For a younger myope I aim to overcorrect them to make them a little hyperopic because, first of all, they're not going to object to being a little hyperopic, and there's a tendency to drift towards myopia over the years," he says. "In an older patient, I'm going to shoot pretty much for plano in the distance eye. In hyperopic patients, I definitely like to leave them plano or just a touch on the hyperopic side because I've found that hyperopic patients hate to be nearsighted in a distance eye. You don't want to overcorrect them—they tend to not like that."

A retrospective study of 345 myopic LASIK eyes[2] treated with a Nidek EC-5000 evaluated the variables that are most likely to contribute to enhancements. It measured the patients' refractive correction, corneal curvature using an Alcon EH-290 topographer, the patient's age and Nidek excimer laser ablation optic and transition zone size, and found the most significant variable contributing to enhancements was an optical zone of 6.5 mm with a transition zone of 7.5 mm. The smaller optical zone was associated with a smaller refractive overcorrection after LASIK surgery (mean for 5.5 mm optical zone, +0.71 +/- 0.29 D; mean, for 6.5 mm optical zone, +1.27 +/- 0.50 D, paired t-test $p<0.0001$). The steeper preoperative corneas had a greater chance of enhancement (mean of sample 44.48 +/- 1.47 D and mean of enhancements 45.30 +/- 1.65 D, $p=0.01$, independent sample test).

Nomograms also have to account for surgical technique, even on the same laser, says Dr. Miller. "Let's say there are two surgeons using the same laser," he says. "Surgeon A lifts the flap and within five seconds is doing the ablation. Surgeon B is a little slower. They lift the flap, admire the beauty of the stromal bed, dry the bed with endless sponges, and overall take 30 seconds before they get around to doing the ablation—so, five seconds versus 30 seconds. After 30 seconds, surgeon B is going to dry out the corneal stromal bed quite a bit, so each pulse of the laser is going to remove more tissue. If both surgeons input -3 D of spherical correction, surgeon B might actually be doing a -4 D correction by the time the cornea is dry. So, that individual's nomogram on the same laser might have to enter less treatment to achieve the desired result."

Most nomograms start producing useful feedback after about 30 cases. "But if you do 30 cases but none of them has a high sphere or high cylinder, you might have to accumulate many hundreds of cases before you realize a benefit for these eyes," Dr. Miller advises.

Shared Nomograms

The surgeons we spoke with say that the nomograms available on laser platforms have improved since the earlier days of LASIK, but they're not perfect.

"As laser technologies mature, these devices do get better at delivering the corrections we desire, but they'll never be perfect," says Dr. Miller. "Some lasers run hotter and take off more tissue per pulse. Some lasers work in environments where the humidity is higher, meaning that as the laser beam travels through the air, moisture in the air steals away some of the energy. The humidity and temperature of the treatment room, altitude, whether patients wear perfume or not—these are things

for which laser manufacturers can't fully compensate."

Dr. Caster encourages doctors to develop their own surgeon-specific nomogram and compare it to the shared nomograms, but with a bias towards the shared nomograms because they involve a lot more data. "Each type of laser will have its own nomogram that will be different, and each individual laser within a type runs slightly different from each other," he says. "That's why a good personal nomogram will be better than the shared nomogram, but the personal nomogram is going to suffer unless you're really accurate at collecting the postop data and you don't have too many people lost to follow-up exams because they're happy."

Despite the value of personal nomograms, not many refractive surgeons are developing their own personal nomograms because it would be technically difficult to do, according to Dr. Miller. "Most tend to use commercial nomogram services," he says. "The commercial nomograms give the surgeon access to data from hundreds or thousands of surgeons using the same laser device. This eases the transition to using a new device. The surgeon gets the benefit of everyone's collective experience with that particular laser. Over time, the surgeon adds data for his or her own site, and the nomogram is improved for their particular use. It should also be remembered that the same laser changes over time. A six-month-old laser is going to run differently than the same laser 10 years later. The optics might get a little dirty; there might be a smudge mark on a mirror somewhere; or the laser cavity may just run colder. Nomograms are designed to keep up with these changes."

Commercial nomograms are exclusive to the laser platform and to the optical zone size. "The program I use is SurgiVision, created by Guy Kezirian, MD," says Dr. Caster. "It's available for Alcon lasers, among others. I think it's a very good program, but you have to be careful to use it properly. For example, with a higher correction, I use the smaller optical zone. For the lower corrections, I use a larger optical zone. I end up with two different formulas: one for the lower corrections and one for the higher corrections. When the data crosses over, the two nomograms will actually get different results. There's judgment involved in using this."

Dr. Caster also performs SMILE procedures and uses the Zeiss Visulyze nomogram service. "With the Zeiss nomogram I was told to start by increasing everything by 10 percent," he says. "That's the nomogram that seems to work and that's what my data has shown. So, my data just confirmed that general rule. It seems a little simpler on the SMILE side with the nomogram."

Dr. McIntire is also familiar with SurgiVision, as well as IBRA (Internet-based Refractive Analysis), both on the Alcon lasers. "They're pretty widely used and it's in the interest of the laser manufacturer that surgeons do a good job with their laser so they provide access to these different nomograms," she says.

> **"Each type of laser will have its own nomogram that will be different, and each individual laser within a type runs slightly different from each other."**
>
> ***— Andrew I. Caster, MD***

"I haven't found a discernible difference in my outcomes when I use one versus the other," continues Dr. McIntire. "If the surgeon has standards set within their clinic, they ought to be able to get reliable outcomes with either one. I think they're both very robust, and there's a large amount of data in both of those platforms. The most important thing is that the information that's going into these algorithms is standardized. Someone might be able to get four or five or maybe more refractions that can get a person seeing 20/20, but if the only guideline in the practice is to enter the refraction that gets the patient seeing 20/20, that doesn't create a standardized process for data collection. There are better ways to do that."

Dr. McIntire uses binocular balanced refraction. "Sometimes, patients can see 20/15, sometimes they can see 20/10, in which case 20/20 is quite blurry for them," she says. "Binocular balance prevents them from being over-minused and gets a very robust, repeatable, accurate refraction that multiple different technicians or physicians could emulate for the same result. There are many methods of using the phoropter and achieving a manifest refraction, and this one takes a little bit more time, but it's robust, it's repeatable. That data would be entered into manifest refraction on IBRA or SurgiVision. It'll ask demographic information and patient name, age, corneal curvature, and give a place to report if there's any other ocular pathology.

"It will want to know the same preop and postop, so you want to enter refraction and best corrected visual acuity and then you'll enter what your target is because the target isn't always plano," she continues. "Planos can see well in the distance without glasses, but sometimes people want to see up close without correction. All of that helps give the algorithm the information that it needs to tell the surgeon 'to get this outcome, this is what you need to program into the laser.' It's going to be somewhere a little bit more or less than what the refraction is just depending on all of the other variables. If there's a new surgeon coming in to use one of these platforms, they don't have any personal historical data to tell them 'here's how my laser operates.' What the program will do instead is create a generalized outcome. It will say, 'based on all of these hundreds of thousands of procedures that have been done by other surgeons in other places, here's a good place to start.' As the surgeon

(Continued on p. 69)

Personalizing Practices with AI

You may be able to improve practice management with the latest AI and smart technology.

ANDREW BEERS
ASSOCIATE EDITOR

Artificial intelligence appears to be the future of many industries and disciplines. Naturally, many individuals are worried about the technology taking over their jobs, but AI, when used properly, has useful applications. For ophthalmology, research on AI technology has leaned more towards clinical applications, such as patient image analysis and diagnosis, but there's more out there. Young physicians ready to start their own practices, as well as established physicians looking to change the way they do things, can implement this technology and other smart solutions to possibly improve their patients' experiences, manage their staff better and even streamline medical coding.

Management Landscape

Anyone leading their own practice or managing a large clinic knows that it's no easy task. John Berdahl, MD, an ophthalmologist at Vance Thompson Vision in Sioux Falls, South Dakota, shares his insight on the current landscape for leading and managing a practice. The issues he brings up may be able to be addressed by the application of new AI systems.

"Medicine is still fundamentally about meeting a person in their moment of vulnerability. It's a people business," says Dr. Berdahl. "You have to have the right people on your team, you have to meet patients where they're at, and you have to be the right person to lead them."

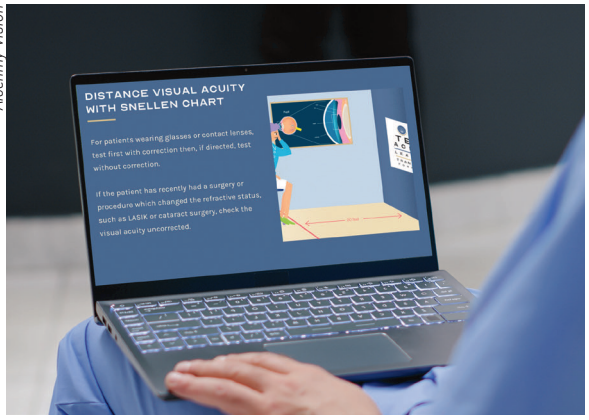
Figuring out how to manage and create the "right team" can depend on the size of the practice. Dr. Berdahl mentions how there's business theory that can explain the limitations of managing a large-scale team. British anthropologist Robin Dunbar suggested that approximately 150 relationships is the cognitive limit for humans, also known as Dunbar's Number,[1] while other data suggests that when you break down relationships on an emotional level, then humans possess the cognitive capacity to maintain hundreds of relationships.[1,2] However, not all practices' teams are staffed with family members and/or best friends, so it can be difficult when leading a team of 100 or more members.

"Either you need to break into additional groups or put in a new layer of management," proposes Dr. Berdahl. "You can see this in Amish culture, and you can also see it in some business structures. I know that Gore of GORE-Tex does this as well. The challenge with adding layers is that it can add bureaucracy, and it's much harder to be a leader that's in the middle, where you have to try to do the work for whoever your boss is and take care of the team below you. They don't quite have the same perceived level of authority, usually, as the leader of the organization.

"I believe the key there is to make sure that the leaders you put in place are the type that can motivate their team," continues Dr. Berdahl. "They know their team, and they've been enabled to make good decisions on behalf of the organization and take great care of their team."

Now, it's important to have a well-rounded team of surgeons, technicians and desk staff to ensure operations run smoothly, but some positions can be harder to fill than others. "I think that technicians are probably the hardest to find because they have a narrower skillset," says Dr. Berdahl. "There's a shortage of surgeons across the country, especially in certain subspecialties. Then, assistants and desk staff have a broader pool to draw from. But I think that one thing that practices lose sight of is that the

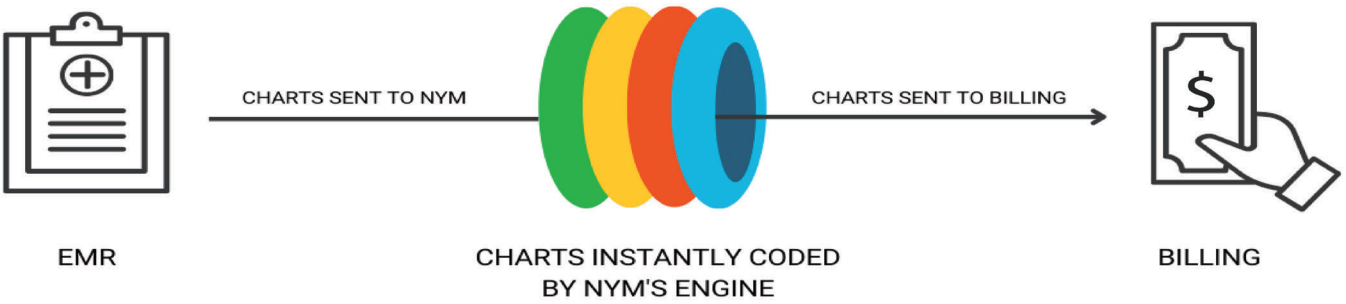
Alchemy Vision



Alchemy Vision offers over 100 videos and resources for training ophthalmic employees. Practices can manage the skills and techniques their staff members learn and set expectations for the new members being trained.

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.



Nym medical coding requires zero human intervention. As illustrated above, physicians facilitate the first steps towards medical coding, completing a patient's EMR. Then, when the physician is ready, they can streamline the coding process by sending the EMR to Nym's coding software. Nym works with major EMR systems, but not all are systems are compatible. Nym is HIPAA-compliant.

biggest reason why somebody wants to work there is if it's a great place to work, and that's based on how people treat each other, and it starts at the top with surgeons."

How can AI get more staff through the door?

TalentGPT with Beamery

Beamery is an online HR suite that allows leaders to hire, connect and manage their staff. This isn't an ophthalmic-specific technology, but Beamery's applications can assist physicians to find candidates that best match their work environment.

In 2023, Beamery announced in a press release that they've launched TalentGPT, a talent acquisition and talent management experience using generative AI. According to Beamery, users can generate new job descriptions that are focused on hiring based on the skills the user deems necessary for their work environment. For example, after HR has added each and every staff member and their skillsets to Beamery, then TalentGPT can assess what roles need to be filled and what skills need to be met. The AI program that allows this to happen is a combination of Beamery's proprietary AI, OpenAI's GPT-4 and other Large Language Models.

Another staffing feature that TalentGPT offers is a candidate pool based on the needs of the business. Once a job description is generated, TalentGPT will provide suggested candidates based on whether they meet the criteria needed or not. Each candidate is ranked by a five-star system, which depicts how well the candidate matches the job description. So, rather than assessing hundreds of candidates for a single position, HR can weed out certain candidates.

Training and Retaining

There are a number of training methods ophthalmologists can employ at their practice. One virtual tool that can enhance training without the need for AI is Alchemy Vision. On their website, they feature three subscription packages: Essential; Professional; and Premium. The Essential package offers more than 40 training videos covering essential skills for an ophthalmic practice and the program outlines the expectations for the position. Additionally, new staff members will be notified to stay on track with their course assignments during training.

The Professional package offers more than 100 training videos along with lectures and a library of study resources. One unique component offered is a badge system and leaderboard to engage the new staff members using a gamification method. This allows members to gain achievements as they move through the training process.

The Premium package includes all of the above, but it is more patient-oriented. This subscription tier pushes staff members to master Alchemy Vision's Patient Centered Solutions model, which is meant to enhance the patient's experience and increase practice revenue.

Communication with Patients

Phone COA and Lumata Health are two programs that can assist with patient communication. It's important to inform patients as much as possible, whether it's preoperatively or postoperatively. "We use technologies to help patients get just-in-time information via text message on what they'll experience throughout their patient journey as a cataract, glaucoma, LASIK or other type of patient," comments Dr. Berdahl.

• ***Phone COA.*** According to the company, Phone COA is a "virtual partner for ophthalmic practice management." A team of virtual technicians reaches out to a practice's patients and captures their information prior to their appointment. The information provided can help preload and prescreen charts and facilitate a seamless transition between EHR systems.

• ***Lumata Health.*** This program is on the postoperative end of ophthalmology. Similar to the idea Dr. Berdahl presented above, Lumata Health ensures patients with diabetic retinopathy, macular degeneration, glaucoma and other ocular pathologies are continuing their regimen, reminded about upcoming visits and are engaged between appointments by contacting them via text or phone call. According to its website, Lumata Health can reduce the number of no-shows by 30 percent.

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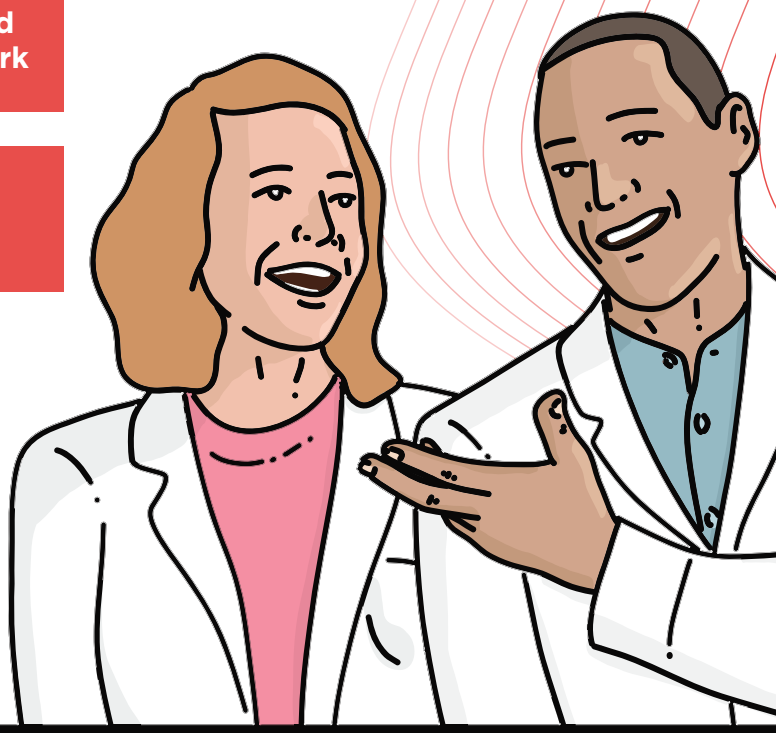

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eyes on EYECARE REVIEW of OPHTHALMOLOGY

AI-Assisted Coding

Medical coding can be streamlined by hiring a medical coder to perform the task, but not everyone has the budget for another staff member. That's where Nym comes in. Nym is an AI medical Coding Engine that assesses a patient's EMR, codes the charts and sends the codes directly to billing. According to the company, Nym's engine has maintained over 95 percent coding accuracy, but that's not perfect. This is where AI technology needs to be monitored.

In a Nym blog post by Hudson Schertz interviewing Amy F. Ho, MD, the complexity of clinical language is addressed. One example provided in the post was on the use of the abbreviation "O.D." For emergency medicine, this stands for "overdose," but in ophthalmology, this means "oculus dexter." While Nym can achieve 95 percent coding accuracy, these are the types of instances where manual monitoring is needed as the engine won't be able to properly decipher the abbreviation unless it's written out.

Future AI Programs

Modernizing Medicine creates specialty-specific EMR solutions for ophthalmologists. The technology they currently employ is intelligence amplification, which is similar to AI, but rather than completing the task, the program offers insight on the best ways to approach the task. Now, Modernizing Medicine is getting ready to implement their own AI technology in its software.

According to a March 2024 press release, Modernizing Medicine will be releasing an AI model to assist with documentation, patient collaboration and claims processing. AI-assisted documentation will assist ophthalmologists with detailed notes during patient visits. AI-assisted patient collaboration will use the technology to message patients in order to improve practice response times for a better patient experience, the company says. This would be a patient self-service where they can book or reschedule appointments, answer routine questions and manage bills without the need for constant phone communication between a practice and its patient. Finally, AI-assisted claims processing will help with flagging denials, which Modernizing Medicine believes will help reduce the burden on staff.

AI technology is incredibly useful, but experts say to be careful. "We do need to be sure that we're using it properly, so we don't just use AI to generate volumes of information that aren't actually helpful for us," says Dr. Berdahl. Hopefully, in the future, practices can become more streamlined with the help of AI-assistive technology. ◀

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DISCLOSURES

Dr. Berdahl has no financial interests to disclose.

(Continued from p. 51)

progressed and topographic-guided PRK was done with CXL," Dr. Jacob mentions. "TGPRK with CXL was done for patients with keratoconus and after a few years a patient's keratoconus progressed and they came to us. The patient had extreme thinning and fortunately it was in the same area where they had CAIRS implanted. Now, since it was so thin, we wouldn't have been able to do a CACXL or CXL directly without CAIRS, but because we already placed CAIRS within this patient, we were able to increase the thickness of the cornea immediately in the thin zone because that was where the CAIRS was implanted, and it could be followed up with cross-linking."

Now, common transplantation adverse events may occur, but Dr. Jacob doesn't view this as an issue. "CAIRS can be associated with complications, but you have to remember that this is a reversible and adjustable procedure. If for some reason the patient doesn't like the visual quality, then you can just reverse it by removing the CAIRS. On the other hand, if you feel that you need to get more or less results, you can also adjust the CAIRS segment easily."

There are many devices and techniques in the pipeline for keratoconus management, but there's more work that needs to be done. Each device mentioned in this article is still undergoing FDA trials and the CAIRS technique is advancing as more researchers introduce novel ways to create incisions, customize ring segments and perform different corneal cross-linking methods. It seems like minimally invasive treatment options for keratoconus are going to continue to grow, and it'll be exciting to see what's next on the horizon. ◀

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How to Manage Optic Pit Maculopathy

Tips for diagnosing and treating these rare anatomical anomalies before they can lead to complications.

BITA MOMENAI, MD, HANA MANSOUR, MD,
MEERA D. SIVALINGAM, MD
PHILADELPHIA PA

Optic disc pits are congenital unilateral excavations of the optic nerve head that may be associated with other abnormalities of the optic nerve and peripapillary retina.[1] Their occurrence is typically sporadic, estimated at one in 10,000 individuals.[1] In cases where the optic pit is asymptomatic, patients are advised to undergo regular follow-up appointments and comprehensive eye examinations, including dilated retinal evaluations.[2] This is crucial, as 25 to 75 percent of cases may develop complications such as associated maculopathy, characterized by retinoschisis-like changes and serous macular detachment.[2]

Given the rarity of optic disc pit maculopathy, however, a definitive consensus on the optimal treatment approach remains elusive. A wide variety of treatment strategies have been described; however, most reports involve a small number of cases with limited long-term follow-up. In this discussion, we'll explore the treatment options available.

Etiology

It's been proposed that optic disc pit maculopathy begins with splitting within the inner retinal layers, similar to macular schisis, and progresses to serous macular detachment following the formation of a hole in the outer retinal layers. This hole allows fluid from within the retina to pass into the subretinal space.[3] Both male and females are equally affected, and maculopathy typically emerges in the third or fourth decades of life, but can affect children also.[1] Patients are encouraged to be aware of the signs and symptoms of maculopathy, such as metamorphopsia, dullness of colors, visual field defects and decreased vision (visual acuity ranges between 20/25 to counting fingers, depending on the extent and duration of maculopathy).[4] They're advised to perform home visual acuity assessments and Amsler grid testing to monitor for potential onset of maculopathy.[5]

Previously, it was advised to allow up to three months for spontaneous resolution before considering surgical options.[6] Spontaneous improvement of optic pit maculopathy, usually following posterior vitreous detachment, can occur in up to a quarter of cases, with potential for visual improvement.[2] Complete spontaneous resolution is rare—although fluctuations in the fluid are common, since the fluid is thought to be connected to the cerebral spinal fluid and vitreous. Visual outcomes can be poor, especially when the detachment is chronic, potentially resulting in permanent vision loss.[2,7] Full-thickness macular holes can lead to irreversible visual impairment, and cystic changes in the foveola and degenerative alterations in the retinal pigment epithelium may also be observed.[3] The integrity of the outer retinal structures is correlated with final visual acuity, making OCT a valuable tool for assessing visual prognosis and the possible need for surgical intervention.[7] Other reports have indicated that the ultimate visual acuity is primarily influenced by the presenting visual acuity.[8] Currently, however, waiting too long without action is generally

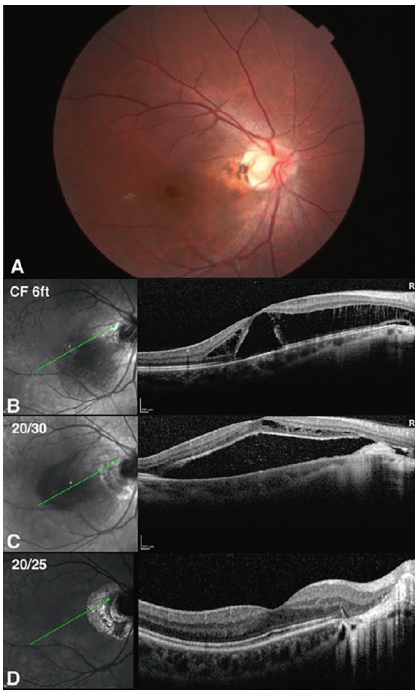

Figure 1. A 36-year-old female with optic disc pit maculopathy OD. Vision was CF 6ft. On presentation (A, B), she underwent focal barrier laser twice, with improvement in vision to 20/30 six months later, however, an increase in subretinal fluid was seen (C). The decision was made to proceed with vitrectomy and SF6 gas tamponade. Vision improved to 20/25 and remained stable (D).

This article has no commercial sponsorship.

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Dr. Yonekawa is an adult and pediatric vitreoretinal surgeon at Wills Eye Hospital / Mid Atlantic Retina, and Associate Professor of Ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University.

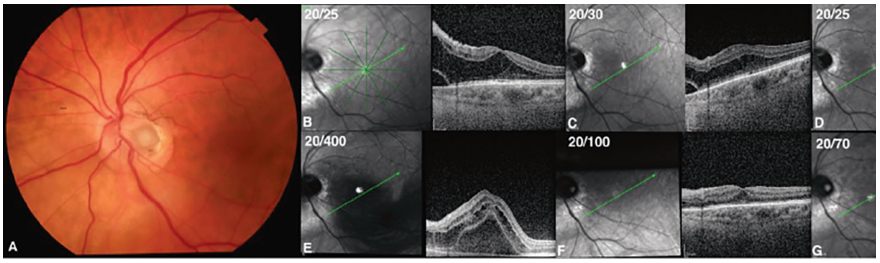

Figure 2. A patient with optic pit maculopathy (A and B: baseline visit) who initially underwent a 25-gauge pars plana vitrectomy, internal limiting membrane peeling and flap technique, endolaser photocoagulation and SF6 gas tamponade. Despite these interventions, the patient's maculopathy and visual acuity worsened over time (C: postoperative month 1, D: postoperative month 3, E: postoperative month 4). Consequently, the decision was made to perform a second surgery, utilizing scleral plugging using a scleral patch graft (Figure 3). In this surgery, additional internal limiting membrane was mobilized. Scleral patch graft was sized, cut and placed within the optic pit. The residual internal limiting membrane flap was then placed over the scleral plug. This combination of treatments led to a significant improvement in the patient's maculopathy (F: postoperative month one, G: postoperative month two).

not recommended, especially if there's evidence of increasing fluid accumulation or deterioration in vision.[2,9]

The Options Explained

The retinal surgeon has several options for these cases:

• ***Laser photocoagulation.*** Laser, applied at the margin of the temporal disc, leads to the formation of a chorioretinal scar that's thought to act as a barrier to prevent fluid from the optic disc pit from continuing to enter the subretinal space.[10] This method involves creating one or several rows of laser burns, aiming for very light burns while minimizing collateral damage to the nerve fiber layer.[1] However, the outcomes of laser treatment have been inconsistent, with an unpredictable—and often long—duration until improvement.[2,10] Additionally, laser over the maculopapular bundle can cause blind-spot enlargement, leading to significant visual field defects. As a result, this method, particularly when used as a standalone treatment, has declined in popularity.

• ***Intravitreal gas injection.*** Injection of intravitreal gas can lead to the formation of a posterior vitreous detachment while simultaneously sealing the optic pit, leading to the reattachment of the macula.[11] However, the success rate for achieving macular reattachment with this technique alone stands at 50 percent, and multiple injections are often required.[11] Combining laser photocoagulation with intravitreal gas injections, on the other hand, has shown potentially more promising results. In one small patient series undergoing this combined treatment approach, there was reported improvement in vision and reduction of fluid in all treated eyes, with a complete resolution of intraretinal and subretinal fluids observed in 75 percent of cases.[12]

• ***Macular buckling surgery.*** This technique involves attaching a buckling element to the sclera along the 6-to-12 o'clock meridian, inducing a buckling effect beneath the macula.[13] Scleral buckling adjusts the direction of posterior hyaloid traction from anterior to posterior, facilitating the reattachment of the macula.[1] Reports indicate that this approach leads to complete fluid resolution in approximately 85 percent of cases, alongside notable enhancements in visual acuity and visual field.[14,15]

Longitudinal studies, tracking patients who underwent this surgery, have shown that buckling's effectiveness persists for more than 10 years, with minimal complications or recurrences and sustained improvements in vision. Furthermore, OCT imaging has confirmed the restoration of the foveal outer retinal layer structure.[16]

While these outcomes are promising, it's important to acknowledge that the surgery requires specialized skills and equipment, including the use of intraoperative B-scan for precise placement of the macular buckle, leading to a limited adoption of this method.[2] Despite being introduced 20 years ago, the technique hasn't become popular, with all published outcomes originating from the same research group.[13,17]

• ***Vitrectomy.*** Recently, the role of vitreous traction has gained recognition as a significant element in the development of optic disc pit maculopathy, leading to pars plana vitrectomy being widely adopted as the main treatment strategy, either alone or in combination with other techniques.[18,19] Induction of a complete posterior vitreous detachment to remove vitreous traction on the optic pit is thought to be a critical step for macular reattachment. However, additional surgical interventions such as laser photocoagulation, gas tamponade, internal drainage and peeling of the internal limiting membrane over the macula continue to be debated. Successful outcomes have been documented using different combinations of these techniques. Time to complete macular reattachment following vitrectomy can be variable and take up to a year to achieve.[20]

• ***Endolaser.*** This approach carries the same risk of laser scar enlargement and visual field defect and should be approached with caution if performed. Gas tamponade has been suggested to help seal the optic pit and displace the subretinal fluid.[18,19] Endodrainage of the subretinal fluid or intraretinal fluid from within the schitic cavities using an intraretinal cannula with or without active aspiration has been also proposed.[17,21] Internal limiting membrane peeling can help to completely eliminate any tangential traction, however the presence of extremely thin internal retinal layers and schisis cavities may increase the risk of iatrogenic macular hole formation during attempts to peel the internal limiting membrane.[22] The value of adding internal limiting membrane peeling to the standard

surgical procedure to enhance surgical and functional outcomes is subject to debate, as good results without internal limiting membrane peeling have also been reported.[3]

• ***Covering/plugging the pit.*** Other surgical techniques include directly covering or plugging the optic disc pit with an internal limiting membrane flap or plug, autologous scleral tissue flap or plug, autologous fibrin from the patient's own blood, fibrin glue or human amniotic membrane.[23-27] Covering the optic disc pit is thought to prevent fluid from leaking into the subretinal space through the pit, yet it doesn't necessarily halt cerebrospinal fluid from infiltrating this space. Plugging the pit with a suitable material is thought to block both potential fluid sources from entering the subretinal area. Risk factors associated with unfavorable surgical outcomes include eyes with fluid present in multiple layers, subretinal fluid that extends beyond the vascular arcades and increased central foveal thickness.[23]

A technique involving the use of an autologous inverted internal limiting membrane flap has been shown to effectively prevent fluid from the vitreous from reaching the subretinal space. This method involves staining and peeling the internal limiting membrane within the temporal arcades while leaving a section near the optic disc edge attached, creating a pedicle-like structure.[28] A small internal limiting membrane flap is sufficient to cover the pit.[29] This approach can lead to quick absorption of subretinal fluid, potentially resulting in early macular reattachment and improvement in visual acuity.[28]

Peeling of the internal limiting membrane flap from the temporal side of the disc and inserting it into the pit with a diamond-dusted membrane scraper is another technique that has been reported. This approach has been applied in cases of chronic or refractory optic disc pit maculopathy, where the pit was sealed with either a relocated or grafted internal limiting membrane flap combined with gas tamponade.[30] An anatomical success rate of 55.6 percent was observed after an average follow-up period of 10 months, with a mean time to reattachment of 6.5 months, and an average improvement in best-corrected visual acuity of three lines.[30] In one comparative case series, filling the optic pit with the internal limiting membrane led to faster fluid resolution compared to merely peeling the internal limiting membrane alone.[31] Nonetheless, both the anatomical and visual outcomes between the two methods were comparable.[31]

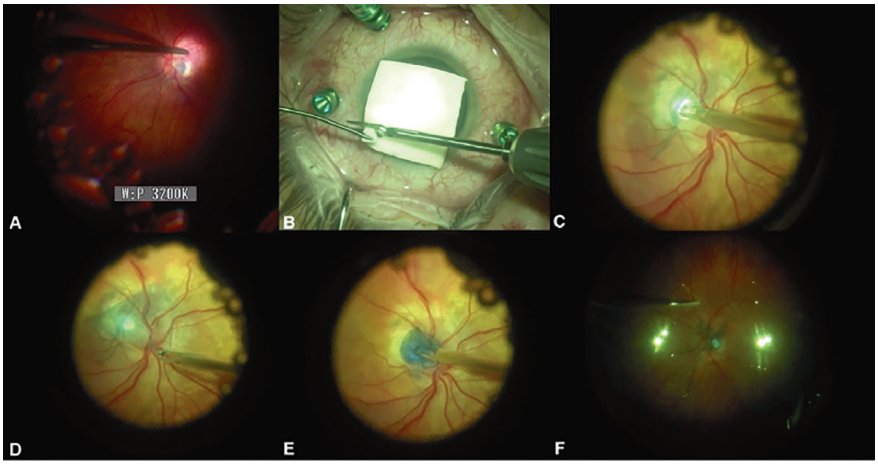

Figure 3. This patient underwent 25-gauge pars plana vitrectomy with endolaser photocoagulation around the pit (A), placement of scleral patch graft plug (B and C), a Brilliant Blue-assisted internal limiting membrane flap (D) and plugging (E), and C3F8 gas tamponade (F).

Autologous scleral flaps can be used to plug the optic pit. In one series, this technique led to successful anatomical results in two of two eyes with prior failed vitrectomy with internal limiting membrane peel, and 17 of 18 eyes not previously treated.[23,32] The addition of the scleral plug is hypothesized to lead to a quicker resolution of subretinal fluid (mean of 4.5 months versus mean of 12 months) and achieves normal central foveal thickness.[32] Similar results have been achieved with a scleral plugs compared to inverted internal limiting membrane flap plug, (85.7 versus 87.5 percent one-year anatomical success, respectively) while ILM peeling alone resulted in suboptimal outcomes in comparison (25 percent one-year anatomical success).[23]

Figure 2 illustrates the case, courtesy of Sunir Garg, MD, of Mid Atlantic Retina at Wills Eye Hospital, of a patient with optic pit maculopathy.

Use of autologous platelet-rich plasma layered over the pit followed by long-acting gas tamponade and face-down positioning was described in a patient with failed prior vitrectomy and endolaser therapy.[33] Subretinal fluid resolution was observed along with significant visual improvement from 20/100 on presentation to 20/50 eight months later.[33] In two reported cases of failed vitrectomy with internal limiting membrane peeling, the authors used autologous fibrin glue to seal the persistent pits.[24] This procedure was successful in achieving retinal reattachment at the final visit at one year in one patient. Final visual acuity was 20/50 from 20/400 on presentation. In the second patient, at two years, final visual acuity was 20/200, stable from preoperative.[24]

Human amniotic membrane patch can also be used to plug the optic pit.[26] In a recent prospective study, 11 eyes of 11 patients underwent 25-gauge pars plana vitrectomy with placement of a human amniotic membrane patch into the optic disc pit, followed by air tamponade.[26] At one-year follow-up, mean visual acuity improved from 20/80 to 20/30 in nine of 11 eyes (82 percent) with complete subretinal and intraretinal fluid resorption and no reported recurrences or complications.[26] However,

longer follow-up and close observation is needed, as one report described a case of human amniotic membrane-plugged optic disc pit that was successful at one year postoperatively with 20/60 vision, however six months later showed recurrence of intraretinal fluid with decline in visual acuity to 20/160.[27]

A combination of intravitreal fibrin glue and internal limiting membrane abrasion has been proposed to treat optic disc pit maculopathy.[25] Internal limiting membrane abrasion is performed as an alternative to internal limiting membrane peeling that aims to reduce damage to subjacent structures. This is followed by the introduction of intravitreal fibrin glue (Tisseel) to seal the optic pit, and gas-air exchange.[25] This technique has been done in only three eyes and only the three months postoperative outcomes have been reported. The long term visual and anatomical outcomes are still unknown.

In summary, diverse surgical techniques have been explored for addressing optic disc pit maculopathy. The choice of technique often hinges on the surgeon's preferences and expertise, alongside the accessibility of medical and surgical materials and equipment. It's crucial to note that while the majority of surgical techniques have been used to attain the intended anatomical and functional results, these improvements typically take several months to attain during the postoperative period. Complete resolution may take up to six to 12 months, and the timeframe is contingent upon the specific surgical technique employed.[23] In instances of refractory cases, re-operation remains a viable option, and successful outcomes following re-operation have been reported. ◀

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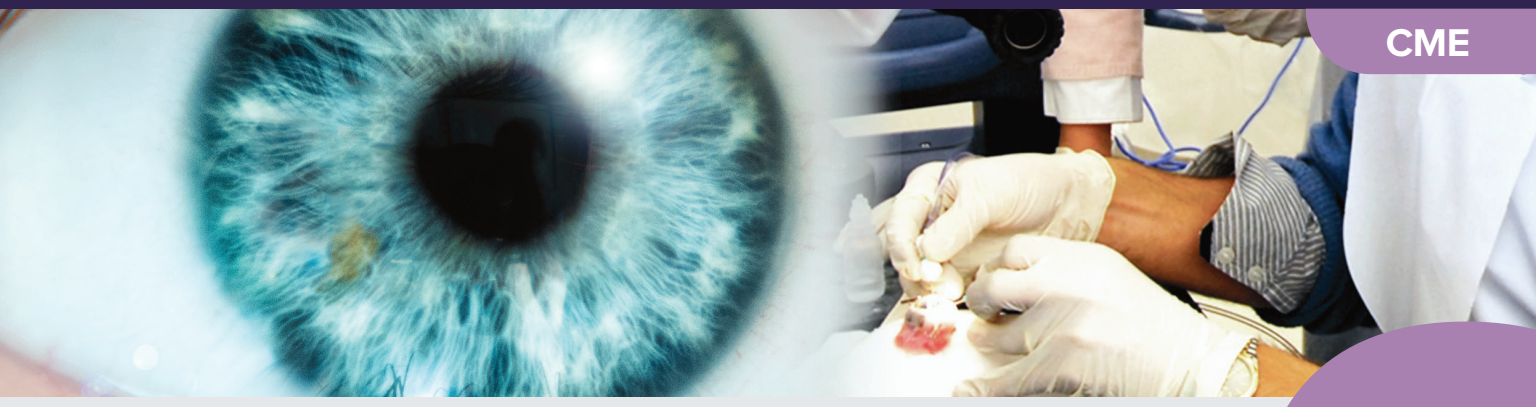

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OCTA in Glaucoma: A Valuable Tool

This modality complements structural OCT and can lead to better disease diagnosis and management.

LUCY Q. SHEN, MD
BOSTON

Optical coherence tomography angiography generates high-resolution images of the microvasculature by using high-speed OCT to repeatedly scan an area and detect the movement of red blood cells, using blood flow as an intrinsic contrast agent of blood vessels. Coupled with structural imaging, it provides us with a unique perspective of the blood vessels at different tissue layers. OCTA is emerging as a valuable tool in the diagnosis and management of glaucoma, particularly in cases of pre-perimetric glaucoma, glaucoma with high myopia, glaucoma with paracentral loss and advanced glaucoma. Here, I'll discuss the advantages and limitations of OCTA, its role in different stages of glaucoma and its potential to complement structural OCT in improving the diagnosis and management of glaucoma.

Regions of Interest

There are three regions of interest for OCTA in glaucoma:

1. Superficial peripapillary region. This region extends from the internal limiting membrane to the retinal nerve fiber layer/ganglion cell layer. Structural OCT is first used to guide the selection of this layer for OCTA imaging. Then, large blood vessels are removed to focus on measuring vessel density of the microvasculature.

2. Choroidal vasculature. The parapapillary choroidal region extends from the retinal pigment epithelium to the choroid.

3. Superficial macular vasculature. This region extends from the internal limiting membrane to the inner plexiform layer.

Useful Settings

OCTA can come in handy when structural OCT falls short in situations such as diagnosing per-perimetric glaucoma, glaucoma with high myopia, glaucoma with paracentral loss and advanced glaucoma.

• ***Pre-perimetric glaucoma.*** OCTA can be a useful adjunct for diagnosing glaucoma in patients who haven't yet demonstrated visual field loss. In this pre-perimetric population, the superficial peripapillary vessel density is decreased compared to the normal population. Based on one study, OCTA performed better than structural ganglion cell complex OCT to diagnose pre-perimetric glaucoma.[1] Another study reported better diagnostic accuracy with OCTA than RNFL OCT.[2] Other studies have shown similar performance between OCTA and structural OCT. OCTA is at least comparable to structural OCT, and may at times be more useful.

• ***High myopia.*** In patients with high myopia, RNFL OCT can be affected by artifacts, making it difficult to distinguish between true disease-associated thinning and artifacts. In contrast, vessel density doesn't show attenuation in a healthy myopic eye. In an eye with high myopia and glaucoma, OCTA can show a decrease in vessel density in affected areas, indicating deficits due to glaucoma, such as an inferotemporal

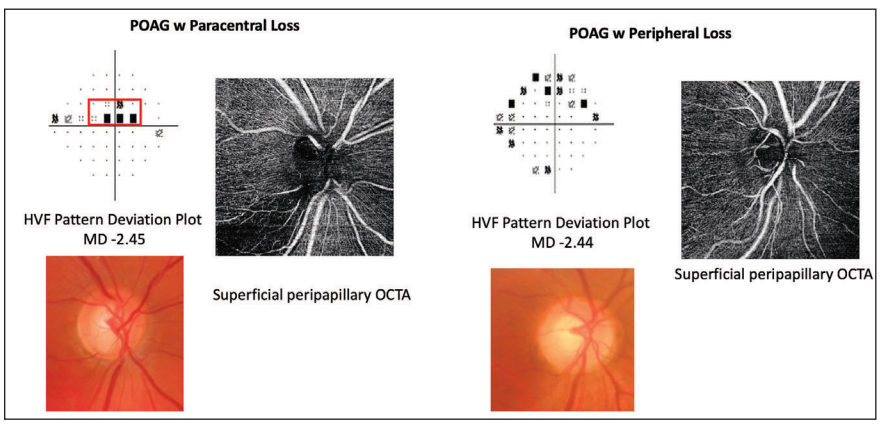

Figure 1. OCTA can detect paracentral loss before structural OCT. In the peripapillary OCTA of the eye with paracentral loss, the vessel density deficit is in the inferotemporal quadrant. In the eye with peripheral loss and similar mean deviation to the eye of paracentral loss, the OCTA doesn't show any obvious defect in the peripapillary microvasculature.

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defect.[3] It's not an automated algorithm to measure these vessel density deficits, however. The authors who reported the good diagnostic ability of OCTA for discriminating high myopia-glaucoma eyes from healthy high myopia eyes integrated widefield SS-OCT and OCTA scans, ultimately resulting in the OCTA-PanoMap.[3] Furthermore, they examined both the peripapillary region and macular region together and manually graded the OCTA images.

Another study demonstrated that when comparing highly myopic eyes with different glaucoma severities based on visual field, similar amounts of RNFL thinning may be observed, again, due to some of these artifacts with structural OCT in highly myopic eyes. On OCTA, however, peripapillary vessel density seemed to correlate better globally and regionally with visual field loss than peripapillary RNFL thickness, and the authors suggested that this OCTA parameter may be useful in monitoring disease progression in high myopes.[4]

• ***Paracentral loss.*** My colleagues and I performed a study comparing OCTA in 33 POAG patients with paracentral loss (n=15) or peripheral loss (n=18) and 31 controls, all of whom underwent peripapillary SS-OCTA.[5] We found that on OCTA, patients with paracentral loss tended to have clearly indicated microvasculature deficits in the affected hemisphere (p=0.001), whereas in those with peripheral loss, despite having similar mean deviation, a deficit wasn't obvious (*Figure 1*). Our study also showed that OCTA had better correlation with paracentral total deviation (a functional measurement of paracentral loss) compared to RNFL thickness measured by structural OCT.

In another study, we demonstrated the predictive utility of a combined model of OCTA and structural OCT parameters for severity of paracentral visual field loss.[6] Of the four models we tested to predict affected paracentral total deviation, the one containing minimum BMO-MRW and OCTA flow was superior.

What role does OCTA play for a patient with known paracentral loss based on their visual field? Since OCTA can detect paracentral loss before it's evident on structural OCT, it can be particularly useful for patients who are unable to perform a reliable visual field test, instead of waiting another six months for a repeat visual field to confirm paracentral loss (*Figure 2*).

Others have found that choroidal microvascular drop-out is associated with paracentral loss.[7] Additionally, a deep learning model using OCTA of the superficial macular region showed greater accuracy in predicting visual field loss in the central part (10-2) compared to structural OCT models (R^2 of 0.85, MAE of 1.76 dB).[8]

• ***Advanced glaucoma.*** As glaucoma progresses, macular vessel density tends to decrease. In cases of advanced glaucoma, the GCIPL thickness may reach the floor while macular vessel density continues to decrease in eyes with worse mean deviation.[9] In contrast to structural OCT, OCTA doesn't show a significant floor effect and remains a useful modality for monitoring advanced-stage progression, particularly when mean deviation is worse than -14 dB.

Dynamic Range

Interestingly, OCTA has demonstrated utility at both ends of the glaucoma progression spectrum, from pre-perimetric to advanced disease. However, it's important to consider the number of steps within the dynamic range of a parameter. Although OCT parameters such as RNFL reach the floor earlier than OCTA parameters such as vessel density, there are more steps within the dynamic range of RNFL. Hence,

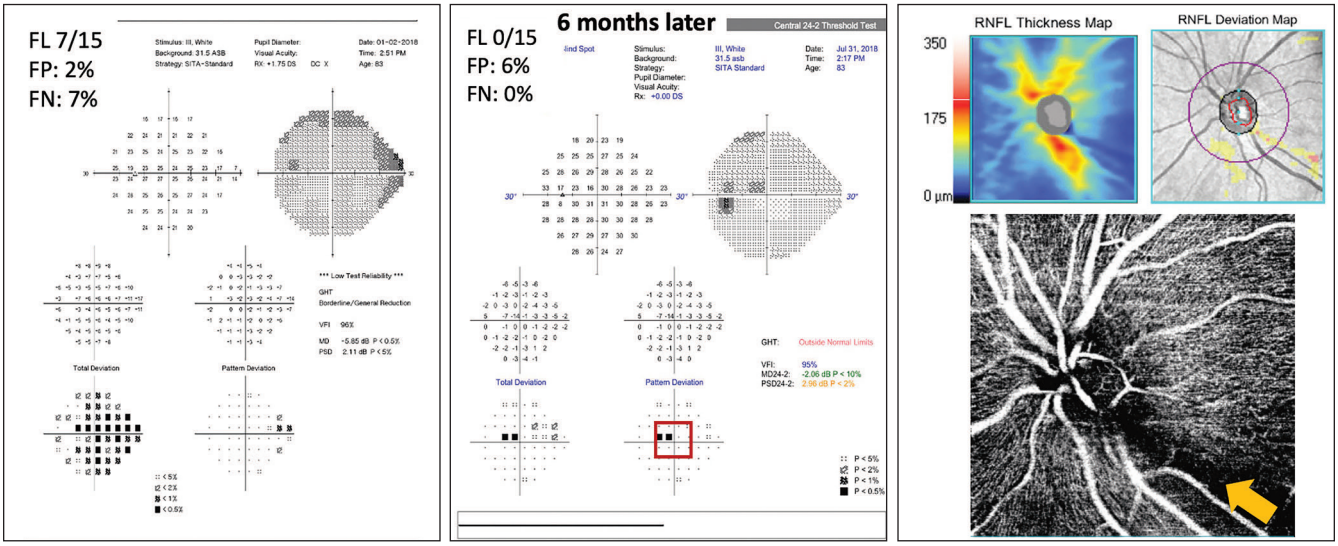

Figure 2. A defect (orange arrow) on OCTA is detectable earlier than on structural OCT in a patient with paracentral visual field loss. Using OCTA may allow for more rapid identification of certain glaucoma subtypes, especially in cases where patients can't perform reliable visual field tests (left). The same patient performed a reliable VF test again six months later, and the paracentral loss was evident (red outline, center).

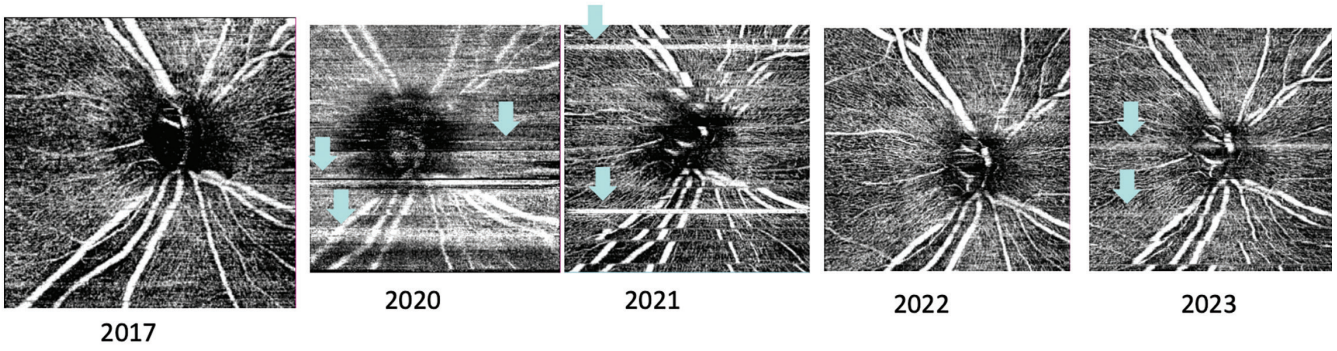

Figure 3. A cooperative study patient with good visual acuity had a series of OCTA scans affected by artifacts over the years, limiting our ability to track progression. Quality scores for years 2017 and 2020 to 2023 were 66, 31, 69, 61 and 70, respectively. A quality score >40 is considered good.

as much as OCTA is helpful for early and advanced glaucoma, we have to consider the fact that its dynamic range may be limited due to inter-visit variability.[10]

Predicting Progression

In addition to aiding diagnosis, baseline OCTA is helpful for predicting glaucomatous progression. Choroidal microvascular drop-out (focal sectorial capillary drop-out) is associated with subsequent disc hemorrhage and progressive RNFL thinning.[11,12] Lower peripapillary vessel density at baseline can also predict progressive RNFL and GCC thinning in POAG.[13,14]

Artifacts

Tracking progression is a different story. OCTA can be affected by artifacts, impacting the quality and reliability of scans. In one study of 5,263 OCTA images, 33.9 percent had poor quality.[15] Of those with acceptable quality (QS ≥4), 23.4 percent had artifacts. A total of 41 percent of glaucoma eyes had artifacts. The most common artifacts were segmentation error, eye movement in healthy patients, blink and Z-offset. HD images had fewer artifacts. Older age, male sex, worse MD, absence of eye tracking and macular scan area were associated with increased chances of obtaining poor-quality scans.

Because of the preponderance of artifacts, OCTA may not yet be useful for tracking glaucoma progression. Figure 3 shows an example of one of our study patients. This patient had good visual acuity and good cooperation, yet many of her images had artifacts over the years, affecting our ability to track progression.

The Bottom Line

OCTA has much to offer glaucoma patients and our burgeoning understanding of glaucoma pathogenesis. We can use OCTA to complement structural OCT.[16] Whenever possible, look at and learn from OCTA images, especially those of patients with high myopia, paracentral loss or advanced disease. OCTA is mainly available on four devices—Triton (Topcon), AngioVue (Optovue), AngioPlex (Cirrus) and Spectralis (Heidelberg)—and most but not all provide automated quantification. However, OCTA measurements from different devices aren't interchangeable. Hence, it's important to use the same device for consistent measurements. Also be sure to understand the limitations of OCTA, including the prevalence of imaging artifacts and its limited ability to track progression over time. ◀

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(Continued from p. 22)

tient to be on systemic immunosuppression.

• ***SLET.*** An alternative to an autograft, simple limbal epithelial transplantation is suited for patients with unilateral injury and one healthy eye. SLET involves the removal of a 2 x 2-mm strip of limbal tissue from the healthy eye. This strip is divided into eight to 12 several smaller fragments, which are then placed epithelium-side up on top of an amniotic membrane covering the entire cornea and adhered using fibrin glue such as Tisseel. A bandage contact lens is placed on top.

Table 2. Roper Hall Classification for Ocular Chemical Injury

Grade	Prognosis	Cornea	Limbal Ischemia
I	Very good	Corneal epithelial damage	None
II	Good	Corneal epithelial damage	<33 percent
III	Guarded	Total epithelial loss, stromal haze, iris details obscured	33 to 50 percent
IV	Poor	Cornea opaque, iris and pupil obscured	>50 percent

Choosing among these procedures depends on the eyes involved, the state of the fellow eye, the patient's preference and the conditions under which the transplant would take place.

As the transplant heals, re-epithelialization will occur and any pannus will begin to regress. Injection will also decrease. When limbal stem cell function is evident, it's then time to determine, based on the severity of the injury, whether or not a full-thickness corneal transplant is needed, such as in cases of significant scarring.

Full thickness corneal transplants for severe chemical injury will have greater likelihood of success after a limbal stem cell transplant has been completed, and with a minimum of six weeks between the two surgeries. In the absolute worst-case scenarios, if a first or even second penetrating keratoplasty isn't effective, a keratoprosthesis may be needed. This is typically a last resort.

In summary, when confronted with ocular chemical injury, it's important to stage the patient and counsel them carefully about all the levels of management that may need to happen. Be sure to emphasize that early management—reducing inflammation, improving the tear film and optimizing the healing environment—is critical for success later on. ◀

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Dr. Palazzolo is a clinical assistant professor at the New York University Grossman School of Medicine Department of Ophthalmology. She's also the medical director for ophthalmology at the NYU Langone Hospital, Long Island; NYU Langone Ambulatory Care, Garden City; and Huntington Medical Group. She has no related financial interests.

(Continued from p. 56)

enters more data, it will eventually rely on the surgeon's own outcomes to tweak their nomogram."

The next most important step is the postop data. "Again, if technicians are only checking the 20/20 line, that's not sufficient," Dr. McIntire says. "Ideally, we'll be doing another postop binocular balance refraction on everybody a few weeks after surgery and using that for the postop data. Over time with volume, these nomograms will help each surgeon and each laser calibrate the nuances from one machine to another, because they're not all exactly the same—they're pretty darn close. So if all you want to achieve is 'good,' then they're pretty close, but if you want 'excellent,' and you want repeatable, reliable excellence, then these numbers become really important."

Artificial intelligence is going to play a bigger role in nomogram development. "I think the future of nomogram development lies in artificial intelligence," says Dr. Chu. "The ability to gather data across multiple platforms and multiple surgeons in different environments and analyze those variables to provide real-time automated information to guide the treatment is the future of nomogram development. Integrating clinical measurements such as topographical assessment will also be part of the future."

One study found the AdaBoost machine learning model to perform very well in the prediction of the sphere, cylinder and astigmatism axis nomograms for SMILE with root-mean-square errors of 0.1378, 0.1166, and 5.17 for the sphere, cylinder and astigmatism axis nomograms, respectively.[3] In the analysis of 3,034 eyes, the feature with the highest importance was preoperative manifest refraction for all nomograms, and for the sphere and cylinder nomograms specifically, the surgeon was the next most important feature in outcomes.

No matter what software program or personalized nomogram you choose to use, Dr. Caster emphasizes it all comes down to data collection and common sense. "It's hard to get good data," he says. "First of all, your happy patients tend to come in less often and they often drop out, therefore your nomogram is going to be biased towards the unhappier patients. You have to spend a lot of time with every refraction that you're going to use in your nomogram analysis and there has to be effort put into that. In general, you have to use nomogram analyses, but you also have to use common sense when looking at the results. If the nomogram is telling you something that your experience tells you isn't right, then I would look at my past experience and factor that in." ◀

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EDITED BY COLLIN ROZANSKI, MD
WILLS EYE RESIDENT CASE REPORT

A patient presents with recurrent right eye pain and photophobia after combined cataract and minimally invasive glaucoma surgery (MIGS).

BRYCE HWANG, MD, AND LAUREN E. HOCK, MD
PHILADELPHIA

Presentation

A 66-year-old female presented to Wills Eye Hospital with recurrent right eye pain and photophobia four months after combined *ab interno* canaloplasty with the Omni system, Schlemm's canal microstent implantation (Hydrus Microstent), and cataract surgery by an outside ophthalmologist. Ocular history was remarkable for primary open angle glaucoma managed with topical glaucoma medications in both eyes.

After the cataract surgery, she developed persistent iritis in the right eye that was treated with topical steroids. Over the next few months, she tried to taper off topical steroid multiple times without success. Steroid response was noted with the patient's intraocular pressure in the right eye increasing to 26 mmHg while on topical prednisolone acetate.

History

Past medical history included osteoarthritis and hypertension. In addition to the mentioned surgery, her POAG had been treated with selective laser trabeculoplasty in both eyes. Family and social histories were noncontributory. She reported no drug allergies. Oral medications included amlodipine, atorvastatin and alendronate. At the time of presentation her topical medications included brimonidine/timolol two times daily in the right eye, dorzolamide two times daily in the right eye, bimatoprost every evening in both eyes and loteprednol four times daily in the right eye.

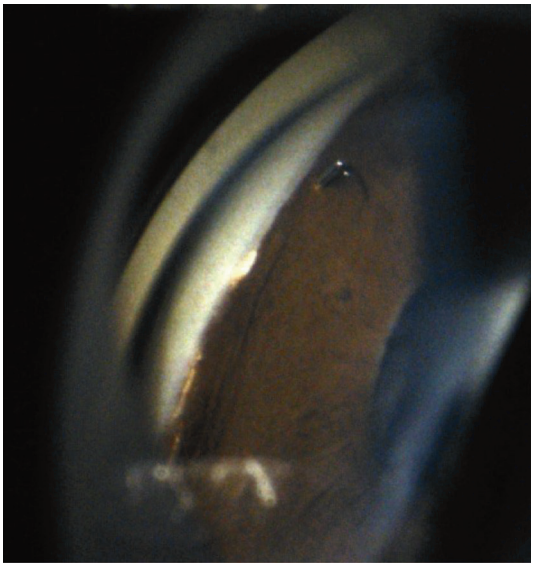

Figure 1. A gonioscopic photograph of the right eye demonstrating the Schlemm's canal microstent inlet incarcerated in peripheral anterior synechiae.

Examination

Ophthalmic examination revealed best-corrected visual acuity of 20/30 in both eyes. The pupils were equally round and reactive to light with no relative afferent pupillary defect. Her IOP was 18 mmHg OD and 13 mmHg OS. Confrontation visual fields and extraocular motility were full OU. Anterior segment examination of the right eye was notable for diffuse corneal endopigment, superonasal and inferotemporal limbal relaxing incisions, trace pigmented cell in the anterior chamber, a one-clock-hour inferior iridodialysis and a PCIOL that appeared to be in the capsular bag.

Anterior segment examination OS was notable for 2+ nuclear sclerotic cataract. Gonioscopy OD showed an inferior iridodialysis and a nasal Schlemm's canal microstent with surrounding peripheral anterior synechiae and protrusion of the stent inlet into the anterior chamber. The microstent inlet was noted to be partially incarcerated in iris tissue *(Figure 1)*. The iridocorneal angles were otherwise noted to be open to the scleral spur OU. Dilated fundus examination showed a cup-to-disc ratio of 0.65 in the right eye and 0.45 in the left eye without disc notching, pallor or hemorrhage.

What's your diagnosis? What management would you pursue? The case continues on the next page.

Work-up, Diagnosis and Treatment

Optical coherence tomography of the peripapillary retinal nerve fiber layer demonstrated inferotemporal thinning OD and no thinning OS. OCT of the macula was within normal limits OU. Automated perimetry with the Octopus perimeter (Haag-Streit) revealed an inferior nasal step OD and non-specific defects OU. Ultrasound biomicroscopy was notable for an inferior iridodialysis, an open iridocorneal angle, a PCIOL centered in the capsular bag and a nasal Schlemm's canal microstent OD *(Figure 2)*.

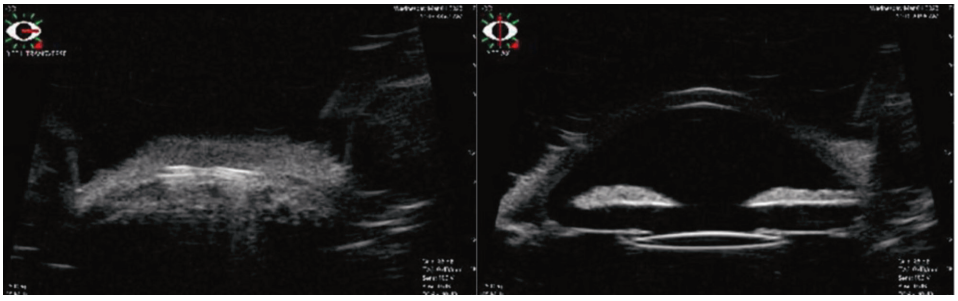

Figure 2. Ultrasound biomicroscopy demonstrating nasal microstent, and inferior iridodialysis, and well-positioned PCIOL in the capsular bag

The differential diagnosis for this case includes postoperative rebound iritis, uveitis-glaucoma-hyphema syndrome from microstent malposition, and infectious or autoimmune etiologies or anterior iritis. Given the posterior malposition of the Schlemm's canal microstent, the leading diagnosis was stent-iris chafing causing UGH syndrome.

Multiple additional attempts were made to taper topical steroids OD and a topical non-steroidal anti-inflammatory drop was added OD. However, the patient experienced rebound of pain and photophobia with each attempt to discontinue topical steroids. Subsequent examinations of the right eye revealed IOPs ranging from 18 to 31 mmHg and persistent trace pigmented cells in the anterior chamber despite use of maximum tolerated topical glaucoma medications.

Given the patient's persistent anterior uveitis and uncontrolled IOP with topical steroid use, the patient was offered removal of the malpositioned Schlemm's canal microstent with possible iris repair OD. The possibility of concurrent glaucoma filtering surgery was also discussed, but the patient elected to proceed with microstent removal alone to see if her IOP would improve with treatment of the stent-iris chafing.

Microstent removal was performed under direct gonioscopic visualization. Viscoelastic was used to free peripheral anterior synechiae from the microstent inlet *(Figure 3)*. A microvitreoretinal blade was then used to lyse remaining synechiae around the microstent scaffold so that it was no longer incarcerated in iris tissue *(Figure 3)*. MicroSurgical Technology (MST) forceps were then used to remove the microstent from the eye with a resulting 3-clock-hour goniotomy *(Figure 3)*. No additional iridodialysis was created during this procedure.

Postoperatively, the patient's vision improved to 20/20 OD, and she was able to taper topical lotedprednol to one drop every 48 hours, but her IOP remained uncontrolled, with intermittent elevations as high as 25 mmHg OD. She was referred to a uveitis specialist for consideration of other etiologies of anterior uveitis, but no additional workup was recommended. Repeat OCT RNFL demonstrated progressive thinning inferiorly and superiorly in the right eye. Her visual fields remained stable OU. Given the concern for glaucomatous progression, the patient was recommended to undergo filtering surgery in the right eye.

Discussion

The Hydrus Microstent (Alcon/Ivantis) is an *ab interno* trabecular microbypass stent that received FDA approval in August 2018 for implantation during phacoemulsification in cases of mild to moderate primary open-angle glaucoma. The biocompatible titanium and nickel alloy stent is 8 mm in length and 290 µm in diameter, featuring three posterior windows and an inlet in the anterior chamber. The HORIZON study demonstrated its superiority over phacoemulsification alone in a prospective cohort study of 546 patients with mild to moderate POAG, showing greater improvements in unmedicated IOP and a reduction in the number of hypotensive eye drops at both 24 and 60 months.[1-3]

Ab interno Schlemm's canal viscodilation (Omni/Visco360, Sight Sciences) is another minimally invasive glaucoma surgery used for treating mild to moderate primary open-angle glaucoma in conjunction with phacoemulsification. In a study of 106 eyes, there was a reduction in IOP and the number of hypotensive eye drops with this technique.[4] The combined use of the Schlemm's canal microstent with additional canaloplasty during cataract surgery may lead to further reductions in IOP. However, studies have inconsistently demonstrated its benefit, with one study showing no change in medicated IOP but a possible reduction in the number of ocular hypotensive medications.[5] Other *ab interno* trabecular microbypass stents (iStent) combined with canaloplasty at the time of phacoemulsification also failed to conclusively demonstrate a benefit in IOP or hypotensive eye drop reduction over stent placement without canaloplasty during cataract surgery.[6]

Schlemm's canal microstent malposition has been reported in the literature as a rare cause of UGH syndrome. In two case reports, removal of the device was necessary for the resolution of intraocular inflammation.[7,8] Notably, in both reports, patients

Figure 3. Intraoperative photographs demonstrating viscodissection, lysis of iris adhesions with an MVR blade, and removal of the microstent from the anterior chamber.

required further filtering surgery for adequate IOP control.[7-8] In the five-year follow-up of the HORIZON study, device malposition was noted in 1.4 percent of cases, with inflammation requiring steroids for more than a month in 5.9 percent of cases.[1-3] However, none of the devices was noted to have migrated after implantation or ultimately require explantation.[3] A review of the FDA Manufacturer and User Facility Device Experience (MAUDE) database between 2009 and 2019 noted four instances of iris-stent touch.[9] In our case, removal of the device led to improvement, but not resolution, of symptomatic iritis.

In conclusion, device malposition causing symptomatic iritis is an uncommon complication of Schlemm's canal microstent placement. Removal of the implant may be necessary to control intraocular inflammation. However, this may not always lead to the resolution of inflammation, and longer-term steroid use coupled with glaucoma filtering surgery may be required. ◀

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Ocular or Periocular Infections
SYFOVRE is contraindicated in patients with ocular or periocular infections.
Active Intraocular Inflammation
SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

PATIENT COUNSELING INFORMATION

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

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

SYF-PI-30NOV2023-2.0

12/23 US-PEGGA-2200163 v4.0

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

GA unravels so much

Save retinal tissue by slowing progression[1-3]

INDICATION

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

IMPORTANT SAFETY INFORMATION

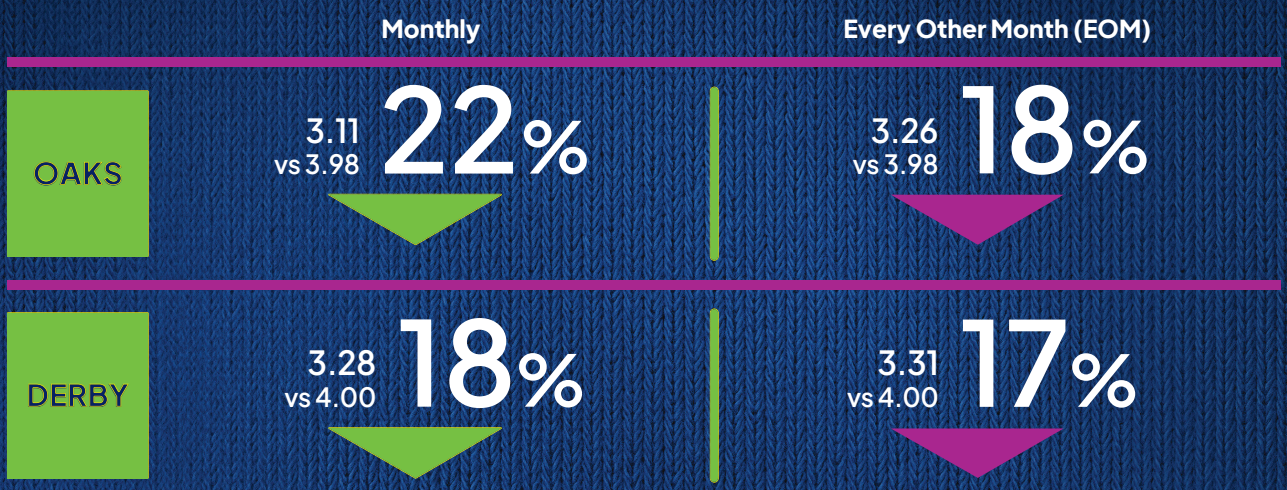
CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- **Retinal Vasculitis and/or Retinal Vascular Occlusion**
  - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

SYFOVRE achieved continuous reductions in mean lesion growth rate* (mm^2) vs sham pooled from baseline to Month 24[1]



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

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

Explore the long-term data

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.
- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

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

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

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

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

Apellis

INTERVENTIONAL GLAUCOMA

SHATTERING THE STATUS QUO

Introducing

iDose® *TR*

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The catalyst to advance the interventional glaucoma revolution, helping you and your patients take back control of their treatment journey.

iDose TR is a long duration intracameral procedural pharmaceutical that delivers prostaglandin analog therapy for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.[1]

Actual size
1.8mm x 0.5mm

1. iDose TR (travoprost intracameral implant) 75 mcg Prescribing Information. Glaukos Corporation. 2023.

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INDICATIONS AND USAGE
iDose TR (travoprost intracameral implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION

DOSAGE AND ADMINISTRATION
For ophthalmic intracameral administration. The intracameral administration should be carried out under standard aseptic conditions.

CONTRAINDICATIONS
iDose TR is contraindicated in patients with active or suspected ocular or periocular infections, patients with corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy, corneal guttatae), patients with prior corneal transplantation, or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]), patients with hypersensitivity to travoprost or to any other components of the product.

WARNINGS AND PRECAUTIONS
iDose TR should be used with caution in patients with narrow angles or other angle abnormalities. Monitor patients routinely to confirm the location of the iDose TR at the site of administration. Increased pigmentation of the iris can occur. Iris pigmentation is likely to be permanent.

ADVERSE REACTIONS
In controlled studies, the most common ocular adverse reactions reported in 2% to 6% of patients were increases in intraocular pressure, iritis, dry eye, visual field defects, eye pain, ocular hyperaemia, and reduced visual acuity.

Please see full Prescribing Information.
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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