Wills Eye Resident Series: A young woman presents with atypical uveitis, *p .87*

REVIEW of OPHTHALMOLOGY®

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BIG DATA AND OPHTHALMOLOGY

Compiling and analyzing huge quantities of real-world data is having a significant impact on practice. **P. 66**

ALSO INSIDE:

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

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

†The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle controlled studies (N=2133). Patients were dosed twice daily. The mean age was 59 years (range, 19-97 years). The majority of patients were female (76%). Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported EDS on a visual analogue scale of 0 to 100). Effects on symptoms of dry eye disease: a larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease: at day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 out of the 4 studies.[1]

Indication

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

Important Safety Information

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

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

KEN JEONG,
REAL DRY EYE PATIENT.

xiidra® (lifitegrast ophthalmic solution)5%

Dry eyes deserve a change

Important Safety Information (cont)

- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

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

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

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

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

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

6.2 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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NEWS

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JULY 2021

Beovu's Future: Reasons for Uncertainty—and Hope

The future of Beovu (brolucizumab, Novartis), the long-term anti-VEGF treatment associated with new reports of safety concerns, remains a source of uncertainty but continued hope among retinal specialists. On May 28, Novartis terminated three trials of shorter-term dosing of the injectable for the treatment of neovascular age-related macular degeneration. The MERLIN trial, which had been comparing the four-week dosing of 6-mg treatments of Beovu to the four-week dosing of 2-mg treatments of Eylea (aflibercept, Regeneron), was ended because of higher rates of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion, the company said.

Novartis has also terminated the RAPTOR and RAVEN studies, which were evaluating the efficacy and safety of Beovu when used to treat retinal vein occlusion with a regimen that included six initial monthly injections. The action by Novartis didn't affect Beovu's continuing Food and Drug Administration approval of Beovu to treat nAMD at 8-to-12-week intervals after three loading doses. Some retinal specialists expressed uncertainty over Beovu's future because reports of safety concerns were resurfacing a second time, following initial reports of IOI in the spring of 2020, less than six months after FDA approval.

"Beovu has superior drying performance compared to Eylea in challenging AMD cases," says Steve Charles, MD, clinical professor of ophthalmology at the University of Tennessee Hamilton Eye Institute. He adds, however, "the inflammation issue puts a cloud over the agent's future. We were hoping for this agent to help with the treatment of DME, proliferative diabetic retinopathy and retinal vein occlusion."

ASRS immediate past president Timothy G. Murray, MD, MBA, notes that the announcement by Novartis has left many retinal specialists feeling uncertain. "We're uncertain at this point as to what it means going forward," says Dr. Murray, who was ASRS president when the society's ASRS Research and Safety in Therapeutics (ReST) Committee combed through Beovu's pre-approval trial data to identify the initial concerns over IOI complications in 2020. He also served as an advisor to the Novartis Safety Review Committee, which further investigated the issues. After the SRC probe, Novartis concluded that there was a confirmed safety signal of rare adverse events. One of the findings showed that retinal vasculitis, retinal artery occlusion or severe vision loss occurred in 8.75 to 10.08 out of 10,000 injections (between February 28 and March 27 of 2020).

"I don't think it was surprising to any of us that there were inflammatory alterations or cases of intraocular inflammation post-injection," says Dr. Murray. "We had seen this tendency to a much lesser degree with the use of other advanced biologics. What we really hadn't seen before was this vaso-occlusive phenomenon, of occlusive vasculitis."

Meanwhile, he says, discussion through Novartis' SRC also focused on the Phase III KESTREL and KITE studies of 6-mg doses of Beovu for treatment of DME compared to treatment with 2-mg doses of aflibercept. "There was some discussion as to whether those trials should continue or not, knowing that there was this issue of occlusive vasculitis," he says. "It was decided to broaden the discussion with the patients enrolled in the studies during informed consent and to continue with the trials. Some specialists felt that was not acceptable and there's been lot of contentious discussion. I feel differently. I treat a lot of patients with off-label indications because I have an unusual oncology practice, and I'm treating tumor patients or pediatric patients or really rare diseases, where there are no FDA drugs that meet those indications."

On May 1, one-year results of the KESTREL and KITE studies showed both had met their primary endpoints of non-inferiority in

(Continued on p. 14)

CORRECTION

In the June article, "Dry Eye: What's in the Pipeline?" Surface Ophthalmics' SURF-200 is described as containing 2% betamethasone, but the concentration is actually 0.2%. *Review* regrets the error.

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

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FEATURES

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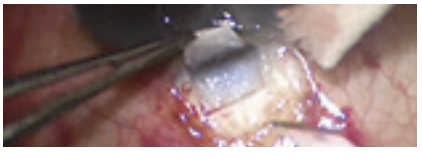

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IMPORTANT SAFETY INFORMATION

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

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

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

*Photrexa® Viscous and Photrexa® are manufactured for Avedro. The KXL System is manufactured by Avedro. Avedro is a wholly owned subsidiary of Glaukos Corporation.

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

MA-01953A

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REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

The Aduhelm Effect

The recent Aduhelm FDA approval debacle, unfortunately, has the potential to be a gut-punch to ophthalmologists in a couple of ways.

First, there's the approval itself. While ophthalmologists have had to wait a decade for FDA approval of various treatments that were already being used in other countries, Aduhelm, an Alzheimer's drug, won a relatively quick approval despite multiple questions about its efficacy. In fact, the FDA's Peripheral and Central Nervous System (PCNS) Drugs advisory committee voted nearly unanimously against approval of Aduhelm. The panel said it saw a lack of efficacy in preventing cognitive decline. In a stunning turn, though, the agency went ahead and approved it anyway, based on the biomarker of amyloid-beta plaques.

Three of the panelists resigned after their input was apparently ignored. One of the panelists, Harvard University professor Aaron Kesselheim, MD, called it, "probably the worst drug approval decision in recent U.S. history."[1]

Aduhelm's second blow to ophthalmologists may prove to be more palpable: Despite having questionable efficacy, Medicare is expected to pay $56,000 for a year's worth of Aduhelm. Of course, other treatments of rare diseases are expensive, but Alzheimer's isn't rare. By one estimate, if only a quarter of the U.S. Alzheimer's patients used Aduhelm, it would cost the system $29 billion. For perspective, this amount represents 78 percent of Medicare's total spending on Part B drugs in 2019, and is five times the FDA's entire budget .[2] Of course, if the drug were highly effective in patients, this probably would be worth it. However, as the panel noted, the efficacy is debatable.

What effect could this amount of spending have on reimbursements for other interventions, such as cataract surgery? CMS persists in lecturing surgeons about the need to be efficient and economize; it enacted a 15-percent reimbursement cut for cataract surgery in 2020, and that was without a $29-billion drug looming.

In the fact sheet CMS circulated to announce the 15-percent cut to cataract surgeons' reimbursement, it stated, "The 2020 PFS final rule is one of several rules that reflect a broader Administration-wide strategy to create a healthcare system that results in better accessibility, quality, affordability, empowerment, and innovation." If this is true, then it's time for CMS to put its money where its mouth is and take a hard look at whether it's worth bankrupting the system for a drug with so many questions about its true efficacy. CMS should begin the process of a National Coverage Determination on Aduhelm, to determine who benefits from it and who doesn't, to make sure its precious funds are going to the right places. That's how you create a health-care system that results in better quality and affordability.

— Walter Bethke
Editor in Chief

1. Biospace.com. https://www.biospace.com/article/3rd-fda-alzheimer-s-advisory-panel-member-resigns-over-biogen-approval/.
2. https://www.fiercepharma.com/pharma/11-500-co-pays-and-diagnostic-hoops-biogen-s-alzheimer-s-56k-drug-aduhelm-set-to-balloon?

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Beovu's Future

(Continued from p. 5)

change in BCVA from baseline for 6-mg treatments of Beovu versus 2-mg treatments of aflibercept at year one. In KESTREL, Beovu patients gained a mean of 9.2 letters versus 10.5 letters for patients receiving aflibercept, according to Novartis. In KITE, patients getting Beovu gained a mean of 10.6 letters versus 9.4 letters for patients on aflibercept. Ocular inflammation rates in KESTREL were 4.7 percent for brolucizumab 3 mg (including 1.6 percent retinal vasculitis), 3.7 percent for Beovu 6 mg (including 0.5 percent retinal vasculitis), and 0.5 percent for aflibercept 2 mg. IOI rates in KITE were equivalent (1.7 percent) between the Beovu 6 mg and aflibercept 2 mg arms, and no retinal vasculitis was reported. Retinal vascular occlusion was reported in KESTREL for brolucizumab 3 mg (1.1 percent) and 6 mg (0.5 percent), and in KITE for brolucizumab and aflibercept, at 0.6 percent. The majority of these events were manageable and resolved with or without treatment, according to Novartis.

"Prior to the occlusive vasculitis issue, a lot of us looked at Beovu as the key to future success—a drug that's more effective, lasts longer and reduces patients' burden of care because of the extended, treatment-free periods it permits between injections," says Dr. Murray.

Many of his colleagues don't see it that way now. "A considerable number of retinal specialists have said they couldn't use a medication which, unto itself, could cause a patient to lose vision," he explains. "The incidence of vasculitis, once it was identified, was significant enough to be concerning. There has been an amazingly strong push-back from the retina community because we didn't see this event occurring with the use of the other biologics we were using."

Using the unchallenged FDA approval of Beovu for extended intervals between treatments, Dr. Murray says he believes retinal specialists will continue to inject the drug in appropriate cases. Taking a treat-and-adjust approach, he says patients who require more frequent treatments and respond well to them may actually benefit from the monthly intervals that were being studied for the possible treatment of persistent fluid in the MERLIN trial.

"Using clinical trial data, most physicians continue to individualize the care of their patients on a visit-to-visit basis, using OCT analyses, visual acuity, comparative review and patients' subjective statements to decide when the next injection should be," he says. "The position of ASRS hasn't changed from the beginning. We don't have guidelines for specific medications. The position is that physicians and their patients deserve as much knowledge as possible so that they have the ability to make informed decisions. What's pushing this is patients who are unresponsive to other therapies and the need to treat some patients who can't manage their burdens of care."

Dr. Murray says the best hope for the future is identifying risk factors for the inflammation, vasculitis and retinal vascular occlusion found in some Beovu patients, possibly at a molecular level, to enable specialists to safely exclude them from receiving Beovu injections.

Caffeine Intake and Glaucoma Risk

In a recent international, multicenter study conducted by the Icahn School of Medicine at Mount Sinai in New York City, researchers found that individuals with a genetic predisposition to elevated intraocular pressure face a threefold increase in their risk of developing glaucoma if they consume a large quantity of daily caffeine. The researchers were led by Louis R. Pasquale, MD, FARVO, deputy chair for ophthalmology research for the Mount Sinai Health System and system vice chair for translational ophthalmology research in the Department of Ophthalmology at the Icahn School of Medicine.

Previous work by this team demonstrated that the risk of POAG increases with high caffeine intake among those with a family history of glaucoma. This study refines that

discovery by demonstrating that the relationship is only evident in individuals with the highest genetic risk scores for the disease.

Using data from the U.K. Biobank, a large-scale population-based biomedical database, researchers analyzed data from 120,000 individuals between ages 39 and 73 who provided their health records and DNA samples between 2006 and 2010. The participants periodically answered dietary questionnaires focused on their caffeine intake, via both drinks and caffeinated food. They also answered questions about their vision, including personal and family glaucoma history. Three years into the study their vision and IOP were checked.

The research team analyzed potential relationships between caffeine intake, IOP and self-reported glaucoma using multivariable analysis. Then, they included the genetic data by assigning participants an IOP genetic risk score and checking to see if this interacted with the other data. Findings included:

- Overall, a high level of caffeine intake wasn't associated with an increased risk of high IOP or glaucoma.
- However, in participants who were in the top 25th percentile of genetic predisposition to elevated IOP, high intake of caffeine—more than 480 mg, about the amount of caffeine in four cups of coffee—was associated with a 0.35 mmHg higher IOP.
- Perhaps most striking, participants in the top 25th percentile of genetic risk who consumed more than 321 mg of caffeine—about three cups of coffee—had a 3.9-fold higher prevalence of glaucoma than participants in the lowest genetic risk group who consumed minimal or no caffeine.

Elaborating on these findings, Dr. Pasquale notes that the different findings reflect different ways of looking at the data. "Keep in mind that well-designed acute intervention studies find that, on average, caffeine dosing equivalent to a cup of coffee produces an approximately 1-mmHg increase in IOP that lasts 60 to 90 minutes," he says. "In our dataset we assessed the relation between habitual coffee consumption and a point estimate of IOP. Of course, caffeine is consumed throughout the day, not just at breakfast."

Why the relatively small IOP difference between the high-risk, high-consumption group and the low-risk, low-consumption group, when there's a nearly fourfold change in glaucoma prevalence between the same groups? "Remember the phrase 'Every 1 mmHg counts in glaucoma?' " Dr. Pasquale says. "We suspect that exposure to a factor that causes mild increases in IOP throughout the day among genetically predisposed individuals culminates in a markedly increased glaucoma risk. We believe this explains the different impacts of high caffeine consumption on IOP vs. glaucoma prevalence."

Dr. Pasquale admits that almost no patients currently know their individual burden of common genetic loci that are linked to elevated IOP or POAG. "Only a small number of patients know they harbor rare Mendelian variants that are strongly linked to glaucoma," he says. "At the current time, a family history of glaucoma is the best surrogate to having that molecular information in hand, but that will change as this type of result reveals the power of polygenic risk-scoring in glaucoma."

Dr. Pasquale says he believes this data is strong enough to warrant some lifestyle recommendations. "I think it's reasonable to advise people with a family history of glaucoma to limit their coffee consumption to two cups per day," he says.

What's next for this research group? "We plan to examine whether there's a relation between caffeine consumption and structural retinal biomarkers related to glaucoma, and whether this association is modified by a genetic predisposition to glaucoma," he says.

A New Treatment for VKC Arrives

A new prescription treatment for vernal keratoconjunctivitis—the rare and recurrent form of ocular allergy sometimes referred to as "morning misery"—is now available in the United States. Verkazia (Santen), a 0.1% cyclosporine ophthalmic emulsion eye drop, received FDA approval late last month for use in children and adults. The company says its oil-in-water cationic emulsion provides improved bioavailability of cyclosporine.

In two randomized, multicenter, double-masked, vehicle-controlled clinical trials, Verkazia demonstrated improvement in corneal inflammation and ocular itching. Adverse events included eye pain (12 percent) and eye pruritus (8 percent). The company notes that these events were usually transitory and occurred during instillation. ◀

Maximizing SMILE Outcomes

Insights from an expert on how to choose the right patients, master techniques and avoid or manage complications.

MAJID MOSHIRFAR, MD
SALT LAKE CITY

As you may know, surgeons learning how to perform small-incision lenticule extraction can potentially encounter surgical complications while they ascend a steep learning curve.[1] Mishaps may include suction loss, black spots and an opaque bubble layer.[2] But the incidence and consequences of significant complications of SMILE, the laser-based refractive procedure that corrects vision with the removal of a small portion of the cornea, is actually lower than you might suspect, especially when compared to the complications of LASIK. Improvements in technology and techniques, combined with our increased experience with SMILE, have enhanced this already-safe procedure.

Relying on the Zeiss Visumax femtosecond laser, the only laser that can be used for SMILE, I now use the procedure for 40 percent of my refractive surgeries. However, I'd be the first to caution you against performing more SMILE cases for the sake of embracing it as your favored modality. When used properly, SMILE is a safe and effective solution for -1 to -9 D of myopia, with myopic astigmatism up to 3 D. Exceeding this correction range, which some surgeons around the world routinely do, is courting trouble, as is taking an aggressive approach that doesn't respect the risks of causing ectasia, a torn cap or other unwanted outcomes.

In this article, having used and studied SMILE for five years, I'll review some newer techniques that can make the procedure easier to perform and some advantages SMILE has over LASIK. I'll also discuss how to avoid and manage complications and meet my triple objectives of reduced risk, surgical success and predictability.

Promising Start

When LASIK was introduced across the world in the 1990s, surgeons reported many flap complications, incidents of epithelial ingrowth, flap amputations and complications during and after surgery, including diffuse lamellar keratitis. We've learned many lessons from these experiences. That's largely why we now know how to handle many of the similar complications with SMILE, which was approved for use in the United States in 2016 and has been administered to more than 3 million people in around 70 countries. For example, my search of the literature finds that SMILE has been associated with only 11 to 19 eyes with ectasia—a stark contrast to more than 1,450 eyes that have been linked to ectasia in LASIK.

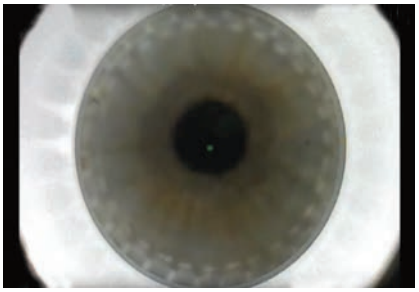

Figure 1. Successfully mastering suction with a femtosecond laser can be a challenge for surgeons learning SMILE, especially if they have no experience creating LASIK flaps.

Besides benefiting from the lessons we've learned from LASIK's longer history, surgeons who successfully provide SMILE do so by thoroughly screening patients and never force-fitting the procedure onto less-than-ideal candidates. As long as you undergo proper training and education, you'll find SMILE to be safe and predictable in these cases.

Patient Selection

Besides a needed correction of -1 to -9 D of myopia and up to 3 D of myopic astigmatism, patients who qualify for SMILE should have a mesopic pupil size that measures less than 7 mm, a residual stromal bed of greater than 250 µm and a central corneal thickness greater than 475 um. Expected post-procedure keratometry should be between 35 D and 47 D, and all patients should have at least a one-year history of a stable refraction within +/- 0.5 D.[3]

We recommend SMILE for patients who play contact sports (at risk for dislocating a LASIK flap), who have mild dry eye (at risk for more severe dry eye after LASIK) and larger pupils (because the SMILE lenticule provides a larger optical zone that

This article has no commercial sponsorship.

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

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INDICATION

DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

WARNINGS AND PRECAUTIONS

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be monitored during treatment.

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

ADVERSE REACTIONS

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

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

References: 1. Sawhney AS, Jarrett P, Bassett M, Blizzard C, inventors; Incept, LLC, assignee. Drug delivery through hydrogel plugs. US patent 8,409,606 B2. April 2, 2013.
2. DEXTENZA [package insert). Bedford. MA: Ocular Therapeutlx, Inc: 2019.

Ocular Therapeutix™

can potentially reduce the amount of induced higher-order aberrations).

Meanwhile, we steer patients away from SMILE if they have epithelial basement membrane dystrophy, corneal opacity, irregular or scarred corneas, irregular corneal astigmatism and ocular allergies. Other contraindications include corneal thinning disorders (such as keratoconus or central corneal thickness less than 475 µm), uncontrolled glaucoma or uveitis, significant cataract, functional monocularity, active eye inflammation or infections, severe dry eye, retinal holes, degenerative retina and macular disease.

Of course, no laser refractive procedures are recommended for pregnant or breastfeeding women because of possible refraction-altering hormonal changes.[3] Also not acceptable are patients with a history of herpes simplex keratitis (unless risks of reactivation are controlled by antiviral treatment) and uncontrolled diabetes (because of delayed wound-healing concerns). To avoid surgical difficulties and poor outcomes, novice SMILE surgeons may postpone doing lower myopic corrections less than -2 D until they've gained some initial experience with at least 20 routine cases of SMILE with higher levels of preoperative myopia, difficult orbital anatomy and high astigmatism, as well as uncooperative and anxious patients, who can disrupt the still environment essential to successful SMILE procedures.[1]

When screening patients, use your slit lamp, pupillometer, corneal pachymetry, computed corneal topography and (if possible) computed videokeratography.[4] Measure the patient's manifest and cycloplegic refraction, refractive stability, and the degree of refractive error and astigmatism.

Besides applying diligent diagnostics to ensure candidates are appropriate for SMILE, you need to make sure they have realistic expectations. Review all risks and benefits, allowing plenty of time to answer questions and to educate them as you obtain informed consent. Patients should know what to expect to hear, feel, see and smell during the procedure, minimizing potential anxiety.

One point to cover with them is the possibility of some myopic regression or hyperopic surprise that may occur after SMILE because we're trying to improve our nomograms over time. PRK can typically be used to correct this. LASIK with a thinner or thicker flap than the orginal SMILE cap is also an appropriate alternative. Some surgeons have the ability to convert the original SMILE cap into a LASIK flap.

Doing It Right

Immediately before SMILE, instill topical antibiotics and proparacaine 0.5%, in both eyes, but avoid using excessive amounts, which can loosen the epithelium and lead to surgically-induced black spots and epithelial defects.[5] Instruct patients to lie on their backs with their necks straight and legs uncrossed, remaining comfortable. Patient cooperation is critical. Provide specific instructions to help them minimize the risk of inadvertently disrupting two core functions

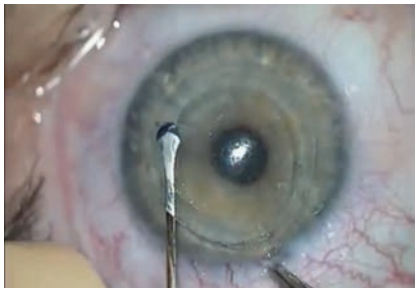


Figure 2. Dissect with care. An untimely dissection into the posterior plane causes the lenticule to adhere anteriorly to the cap.

of SMILE—docking and centration of the laser. They should:

- keep their head as still as possible;
- stay calm;
- fixate their eye on the blinking green light in the laser; and
- keep their eye wide open and still, resisting urges to close it.

After the patient is comfortably situated, you can dock the laser on the first eye and verify that it's properly docked before contacting the cornea with the laser's curved contact glass. Once the laser is centrated, initiate suction and maintain it for the duration of the procedure.

The femtosecond laser generates four sequential pulses that cut through the stromal tissue and create an intrastromal refractive lenticule measuring 6 mm to 6.5 mm in diameter. This is the small portion of cornea that creates the intended correction when it's removed. You'll need to use the laser to make a 3-to 5-mm incision along the superior or superotemporal regions of the cornea. After making all five incisions, which takes less than 24 seconds to complete, use a spatula to separate the residual lenticular appendages along the anterior and posterior planes of the intrastromal bed, and forceps to extract the lenticule.

Most Challenging Part

Extracting the lenticule is typically the most challenging part of the procedure when you're starting out with SMILE. It's better to identify the anterior plane of the lenticule and dissect the lenticule from the cap first, then proceed with the posterior dissection of the lenticule from the residual stromal bed. If you don't recognize the correct tissue plane during removal, and inadvertently dissect the posterior plane, it can be challenging to find the anterior plane of the lenticule.

To avoid this complication, look carefully for the meniscus-shaped gap between the inner ring and the lenticule edge, commonly known as the meniscus sign. The meniscus sign will help you discern the posterior plane from the posterior lamellar channel. Meanwhile, another challenge can arise if you haven't dissected the lenticule in the intrastromal tissue properly, which will compromise your ability to distinguish the lenticule edge from the anterior dissection plane. This can result in a loss of needed countertraction from the corneal stroma.[1]

As our experience with SMILE has progressed, we've seen the development of alternative approaches to lenticule extraction that can spare inexperienced surgeons the challenge of an inadequate result. For example, you can separate the lenticule edge from the overlying cap by employing a "push-up" technique, using an instrument with a Y-shaped tip to engage the lenticule edge and push it up from the stromal bed.

You can also use intraoperative anterior segment optical coherence tomography to identify the dissection planes, which will be hyperreflective, enabling you to more easily recognize where to dissect the tissue. In addition, you can turn to a newer method of lenticule extraction, called lenticuloschisis, in which you peel the lenticule away from surrounding stroma and extract it without using a tissue dissector. I haven't personally used this technique. To use it, you would find the edge of the lenticule and then use the 25- or 27-gauge intravitreal forceps to grasp the edge of the lenticule from its bed in a clockwise or counter-clockwise direction, very similar to the maneuver that we commonly do during capsulorhexis in cataract surgery.

Because this alternative minimally manipulates the tissue, some surgeons say it can produce a smooth interface, earlier visual recovery and better visual quality in the immediate postop period.[6]

Occasionally, you may encounter a lenticule that you're unable to remove. You can meet this challenge by converting the procedure to femtosecond lenticule extraction, or FLEx, a forerunner of SMILE. Using this alternative, you create a corneal flap and, instead of ablating the corneal stroma, you complete the intrastromal dissection and extract the refractive lenticule that way.[7]

Another alternative to standard lenticule extraction is to use customized surface ablation, although this has limitations, including postop haze.[6] In very rare cases, when you can't extract the lenticule, or when a lenticule remnant is retained in the stromal bed postoperatively, your patient may experience irregular astigmatism. For this complication, patients have undergone effective treatment with transepithelial phototherapeutic keratectomy.[4]

Some surgeons may inject the stromal pocket where the lenticule was just removed with special Vision Blue dye or dilute Kenalog and subsequent BSS irrigation to find out if they can see any irregularly stained stromal margin from where the original lenticule was dissected.

Once you've completed surgery, administer topical steroids (dexa-

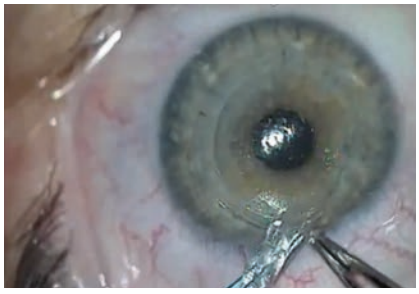


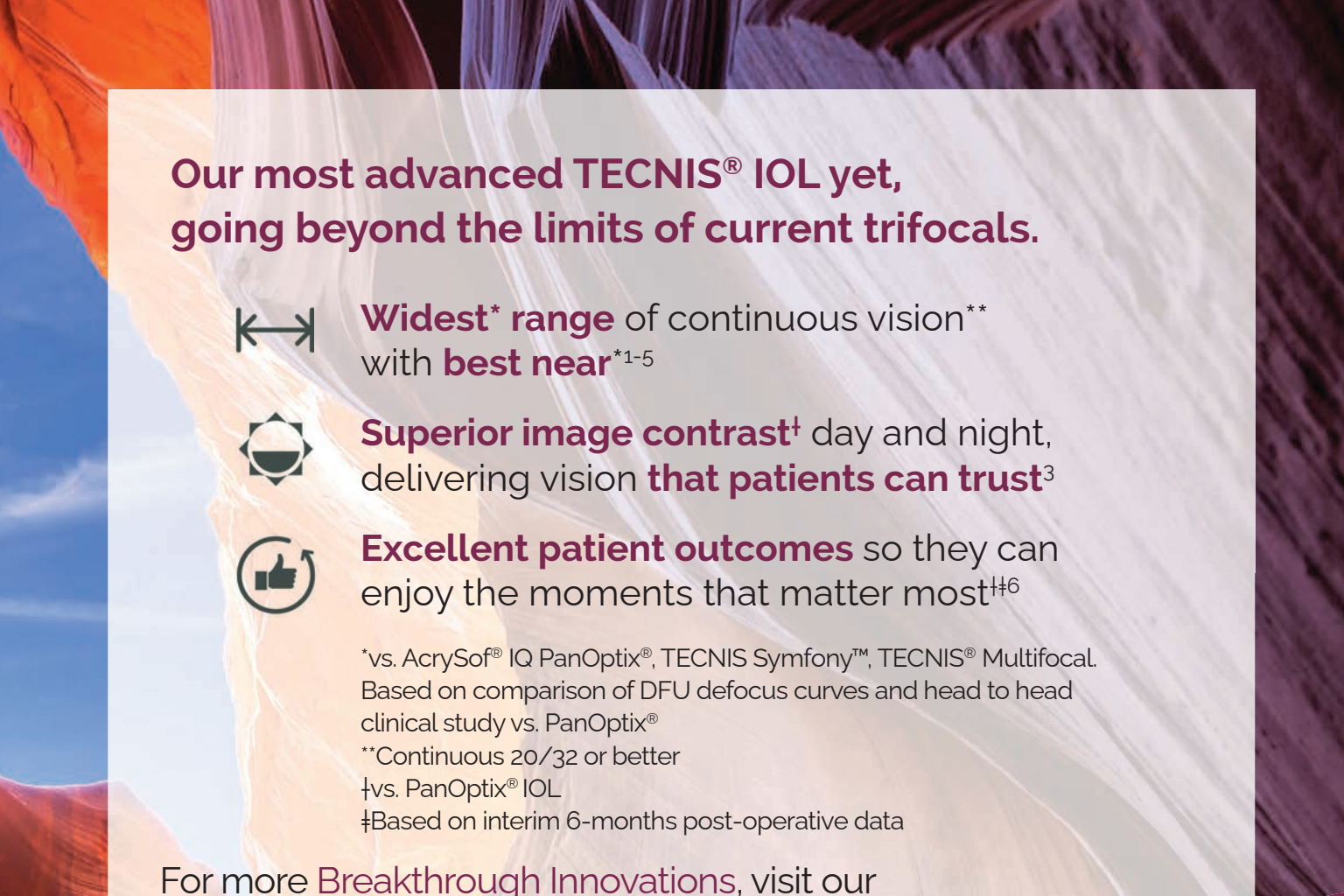
Figure 3. Be careful to completely remove the lenticule, leaving no portion behind in the pocket.

1. TECNIS Synergy™ IOL with TECNIS Simplicity® Delivery System DFU, Z311421E
2. Data on File, Johnson & Johnson Surgical Vision, Inc. DOF2020CT4014 - Forte 1: A Comparative Clinical Evaluation of a New TECNIS® Presbyopia Correcting Intraocular Lens Against a PanOptix® Intraocular Lens- DEFOCUS CURVES AND VISUAL ACUITY RESULTS
3. Data on File, Johnson & Johnson Surgical Vision, Inc. DOF2019OTH4002 - Weeber H. MTF of the TECNIS Synergy™ OptiBlue® IOL, and other lens models. 27 Mar 2019.
4. TECNIS® Multifocal 1-Piece IOL ZKB00 and ZLB00 DfU - US - Doc. #Z311328. Rev. A, 04/2018. REF2019CT4049.
5. TECNIS Symfony™ Extended Range of Vision IOL DfU - US -Doc. #z311215. Rev. 01, 12/2017 REF2020MLT4051
6. Data on File, Johnson & Johnson Surgical Vision, Inc. DOF2020CT4015- Forte 1: A Comparative Clinical Evaluation of a New TECNIS® Presbyopia Correcting Intraocular Lens Against a PanOptix® Intraocular Lens- SPECTACLE WEAR AND SATISFACTION RESULTS

INDICATIONS and IMPORTANT SAFETY INFORMATION FOR TECNIS Synergy™ IOL with TECNIS Simplicity® Delivery System, Model DFR00V and TECNIS Synergy™ Toric II IOL with TECNIS Simplicity® Delivery System, Models DFW150, DFW225, DFW300, DFW375

Rx Only

INDICATIONS: The TECNIS Simplicity® Delivery System is used to fold and assist in inserting the TECNIS Synergy™ IOL which is indicated for primary implantation for the visual correction of aphakia in adult patients, with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The TECNIS Simplicity® Delivery System is used to fold and assist in inserting the TECNIS Synergy™ Toric II IOLs that are indicated for primary implantation for the visual correction of aphakia and for reduction of refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. Compared to an aspheric monofocal lens, the TECNIS Synergy™ IOLs mitigate the effects of presbyopia by providing improved visual acuity at intermediate and near distances to reduce eyeglass wear, while maintaining comparable distance visual acuity. The lens is intended for capsular bag placement only. **WARNINGS:** Intraocular lenses may exacerbate an existing condition, may interfere with diagnosis or treatment of a condition or may pose an unreasonable risk to the eyesight of patients. Patients should have well-defined visual needs and be informed of possible visual effects (such as a perception of halo, starburst or glare around lights), which may be expected in nighttime or poor visibility conditions. Patients may perceive these visual effects as bothersome, which, on rare occasions, may be significant enough for the patient to request removal of the IOL. The physician should carefully weigh the potential risks and benefits for each patient. Patients with a predicted postoperative residual astigmatism greater than 1.0 diopter, with or without a toric lens, may not fully benefit in terms of reducing spectacle wear. Rotation of the TECNIS Synergy™ 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



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possible, prior to lens encapsulation. The lens and delivery system should be discarded if the lens has been folded within the cartridge for more than 10 minutes. Not doing so may result in the lens being stuck in the cartridge. 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. **PRECAUTIONS:** Interpret results with caution when using autorefractors or wavefront aberrometers that utilize infrared light, or when performing a duochrome test. Confirmation of refraction with maximum plus manifest refraction technique is strongly recommended. The ability to perform some eye treatments (e.g., retinal photocoagulation) may be affected by the IOL optical design. The surgeon should target emmetropia, as this lens is designed for optimum visual performance when emmetropia is achieved. The TECNIS Synergy™ IOLs should not be placed in the ciliary sulcus. Carefully remove all viscoelastic and do not over-inflate the capsular bag at the end of the case. Residual viscoelastic and/or over-inflation of the capsular bag may allow the lens to rotate, causing misalignment of the TECNIS Synergy™ Toric II IOL. All preoperative surgical parameters are important when choosing a TECNIS Synergy™ Toric II IOL for implantation, including preoperative keratometric cylinder (magnitude and axis), incision location, the surgeon's estimated surgically induced astigmatism (SIA) and biometry. Variability in any of the preoperative measurements can influence patient outcomes and the effectiveness of treating eyes with lower amounts of preoperative corneal astigmatism. The effectiveness of TECNIS Synergy™ Toric II IOLs in reducing postoperative residual astigmatism in patients with preoperative corneal astigmatism < 1.0 diopter has not been demonstrated. Patients with a predicted postoperative astigmatism greater than 1.0 D may not be suitable candidates for implantation with the TECNIS Synergy™ and TECNIS Synergy™ Toric II IOLs, as they may not obtain the benefits of reduced spectacle wear or improved intermediate and near vision seen in patients with lower predicted postoperative astigmatism. **ATTENTION:** Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

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methasone 0.1%) and topical fluoroquinolone eye drops (moxifloxacin 0.5%) several times daily. Topical corticosteroids may be used up to four weeks postoperatively. You also need to closely follow these patients in the weeks to months after SMILE.

Managing Complications Safely

Besides the initial learning curve of SMILE, beginner surgeons must be familiar with potential intraoperative complications during the procedure.[9] Below is what to watch for and how to respond proactively:

• ***Complications from lenticule creation.*** These can include suction loss, the formation of an opaque bubble layer, subconjunctival hemorrhage, incisional bleeding and black spots. Loss of suction occurs in about 6 percent of cases and is typically due to movement of the patient or the eye.[1,9] If you lose suction when less than 10 percent of the lenticule has been cut, you can re-dock and re-centrate the laser. If more than 10 percent of the lenticule has been cut, you'll need to convert to either PRK or LASIK. Most patients who experience suction loss and are appopriately treated for these complications experience excellent visual outcomes.[5]

The opaque bubble layer, secondary to the accumulation and opacification of bubbles in the intrastromal interface, can be managed intraoperatively by massaging them out of the interface. Use the same SMILE dissector or a spatula very similar in design to a cyclodialysis spatula. This complication can cause delayed visual recovery but doesn't prevent good long-term visual outcomes.

The black spots are from debris or air bubbles that get trapped between the laser's curved contact glass and the cornea. To eliminate them, clean the glass and, as needed, the ocular surface. This issue doesn't typically affect visual outcomes except where the black spot was noted. Surgeons will have more difficulty with the dissection of the two planes form the actual lenticule and care must be taken to avoid lenticule or cap tear.[5]

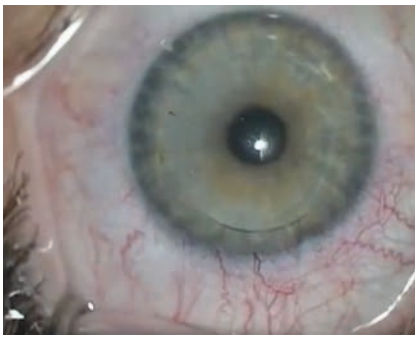

Figure 4. Strict follow-up after SMILE is critical to avoid complications. Prescribe topical steroids and a fourth-generation fluoroquinolone, both q.i.d., for a week, followed by a three-week taper of steroids. The patient is seen after one day, one week, one month, three months and at one year.

• ***Complications from lenticule dissection or extraction.*** Watch for a lenticule remnant, corneal abrasion, lenticule adhesions and incisional tears.

A lenticule remnant and lenticule adhesions can be handled intraoperatively or postoperatively by using the techniques I discussed when addressing the most challenging part of SMILE. Peripheral corneal abrasions, caused by excessive manipulation in 5.5 percent of cases, are more common among surgeons who lack significant experience performing SMILE.[8,9,10] Incisional tears occur in 9.6 percent of patients and may be secondary to surgeon inexperience or the patient suddenly moving the eye while an extraction instrument is inside of the SMILE pocket that was created by the laser. One way to avoid this is to get your patient to relax and to fixate his or her eyes intraoperatively.[8] You can manage corneal abrasions and incisional tears with artificial tears and postop bandage contact lenses. They typically don't affect visual outcomes.[10]

• ***Primary complications.*** Postop dry eye is found in about 3 percent of post-SMILE patients and can be attributed to decreased trophic influences in the corneal epithelium, inflammation, damage to limbal goblet cells during suction and impaired corneal sensation that enables blinking.[7,10] Most studies report fewer dry-eye issues immediately after SMILE than after femtosecond LASIK, as demonstrated in higher levels of tear-film breakup time, corneal sensitivity and corneal nerve regeneration.[10,6] Infectious keratitis, reported in some cases, can be avoided by using a postop antibiotic regimen. Affected patients, usually noncompliant with the postop treatment, should receive prompt irrigation with bactericidal povidone-iodine and an antibiotic solution.[9]

Other rare postop complications include epithelial ingrowth, irregular topography, microstriae and interface inflammation.[7] Meanwhile, all known post-SMILE cases of ectasia have occurred in eyes with diagnosed or undiagnosed forme fruste keratoconus.[11]

Is SMILE Worth Pursuing?

If you don't provide SMILE to your patients, you may be asking yourself if it's worth trying, considering the initial learning curve and potential risks that may intimidate surgeons who are new to the procedure. Indeed, there are challenging issues to consider. Patient discomfort during the intial learning phase of the SMILE may be higher but can be easily addressed with sufficient topical anesthesia, anxiolytics or sedatives.[13] Postop light sensitivity and blurring of vision may affect some SMILE patients. Fortunately these issues typically resolve after three months.[14]

Visual recovery has been reported to be slower in SMILE, but I believe based on my experience that visual recovery for both procedures is very similar. (No significant difference between the two procedures has been documented at six months postoperatively.)[6,7] However, when comparing LASIK to SMILE, we see several potential reasons to use SMILE, including long-term UDVA

(Continued on p. 84)

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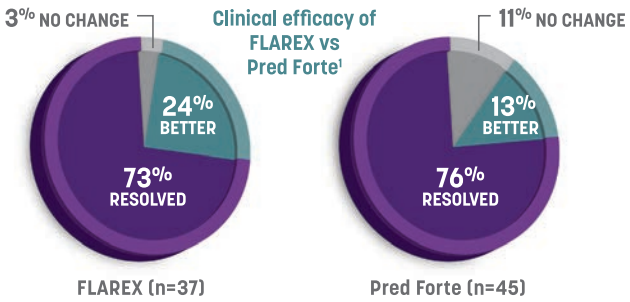

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IMPORTANT SAFETY INFORMATION
ADVERSE REACTIONS: Glaucoma with optic nerve damage, visual acuity and field defects, cataract formation, secondary ocular infection following suppression of host response, and perforation of the globe may occur.
Please see the Full Prescribing Information on the next page.

[a]**STUDY DESIGN:** The efficacy and safety of FLAREX were evaluated in two identical, randomized, double-blind clinical trials. In one trial of 78 patients with ocular surface inflammation (eg, conjunctivitis, episcleritis, scleritis) in one or both eyes, patients administered either FLAREX (n=41) or fluorometholone alcohol (n=37) every 2 hours for the first 2 days and then every 4 hours thereafter, with signs and symptoms of inflammation assessed at Days 1, 3, 8, and 13. In a separate but identical trial in 82 patients with ocular surface inflammation, patients administered either FLAREX (n=37) or prednisolone acetate 1.0% (n=45). At each visit, investigators determined if signs and symptoms in the involved eye were resolved, improved, unchanged, or worsened. If a patient was rated as signs and symptoms resolved before the end of the study, steroid drops were discontinued and the patient was considered to have completed the trial.[1]

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References: 1. Leibowitz HM, Hyndiuk RA, Lindsey C, et al. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. *Ann Ophthalmol.* 1984;16(12):1110-1115. 2. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification report. *Ocul Surf.* 2017 Jul;15(3):276-283. doi: 10.1016/j.jtos.2017.05.008. 3. FLAREX [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2017. 4. US Department of Health and Human Services, Food and Drug Administration. *Approved drug products with therapeutic equivalence evaluations.* (Orange Book). 40th ed. Washington, DC: US Department of Health and Human Services, Food and Drug Administration; 2020. 5. National Center for Biotechnology Information, PubChem. Fluorometholone acetate. https://pubchem.ncbi.nlm.nih.gov/compound/ fluorometholone-acetate. Accessed September 10, 2020. 6. Sendrowski DP, Jaanus SD, Semes LP, et al. Anti-inflammatory drugs. In: Bartlett JD, Jaanus SD, eds. *Clinical Ocular Pharmacology.* 5th ed. St Louis, MO: Butterworth-Heinemann; 2008:221-244.

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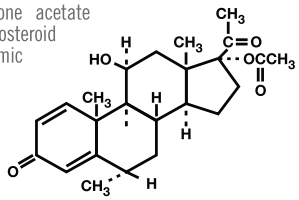
DESCRIPTION: FLAREX® (fluorometholone acetate ophthalmic suspension) is a corticosteroid prepared as a sterile topical ophthalmic suspension. The active ingredient, fluorometholone acetate, is a white to creamy white powder with an empirical formula of C24H31FO5 and a molecular weight of 418.5. Its chemical name is 9-fluoro-11, 17-dihydroxy-6 -methylpregna-1, 4-diene-3, 20-dione 17-acetate. The chemical structure of Fluorometholone Acetate is presented above:



Each mL contains: Active: fluorometholone acetate 1 mg (0.1%). Preservative: benzalkonium chloride 0.01%.

Inactives: sodium chloride, monobasic sodium phosphate, edetate disodium, hydroxyethyl cellulose, tyloxapol, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. The pH of the suspension is approximately 7.3, with an osmolality of approximately 300 mOsm/kg.

CLINICAL PHARMACOLOGY: Corticosteroids suppress the inflammatory response to inciting agents of mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced. Corticosteroids cause a rise in intraocular pressure in susceptible individuals. In a small study, FLAREX (fluorometholone acetate ophthalmic suspension) demonstrated a significantly longer average time to produce a rise in intraocular pressure than did dexamethasone phosphate; however, the ultimate magnitude of the rise was equivalent for both drugs and in a small percentage of individuals a significant rise in intraocular pressure occurred within three days.

INDICATIONS AND USAGE: FLAREX (fluorometholone acetate ophthalmic suspension) is indicated for use in the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.

CONTRAINDICATIONS: Contraindicated in acute superficial herpes simplex keratitis, vaccinia, varicella, and most other viral diseases of cornea and conjunctiva; mycobacterial infection of the eye; fungal diseases; acute purulent untreated infections, which like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; and in those persons who have known hypersensitivity to any component of this preparation.

WARNINGS: FOR TOPICAL OPHTHALMIC USE ONLY. NOT FOR INJECTION. Use in the treatment of herpes simplex infection requires great caution. Prolonged use may result in glaucoma, damage to the optic nerve, defect in visual acuity and visual field, cataract formation and/or may aid in the establishment of secondary ocular infections from pathogens due to suppression of host response. Acute purulent infections of the eye may be masked or exacerbated by presence of steroid medication. Topical ophthalmic corticosteroids may slow corneal wound healing. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with chronic use of topical steroids. It is advisable that the intraocular pressure be checked frequently.

PRECAUTIONS:

General: Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.

Information for Patients: Do not touch dropper tip to any surface, as this may contaminate the suspension. The preservative in FLAREX® (fluorometholone acetate ophthalmic suspension), benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of FLAREX (fluorometholone acetate ophthalmic suspension) but may be reinserted 15 minutes after instillation. Patients should be advised that their vision may be temporarily blurred following dosing with FLAREX (fluorometholone acetate ophthalmic suspension). Care should be exercised in operating machinery or driving a motor vehicle.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No studies have been conducted in animals or in humans to evaluate the possibility of these effects with fluorometholone.

Pregnancy: Fluorometholone has been shown to be embryocidal and teratogenic in rabbits when administered at low multiples of the human ocular dose. Fluorometholone was applied ocularly to rabbits daily on days 6-18 of gestation, and dose-related fetal loss and fetal abnormalities including cleft palate, deformed rib cage, anomalous limbs and neural abnormalities such as encephalocele, craniorachischisis, and spina bifida were observed. There are no adequate and well controlled studies of fluorometholone in pregnant women, and it is not known whether fluorometholone can cause fetal harm when administered to a pregnant woman. Fluorometholone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLAREX (fluorometholone acetate ophthalmic suspension), is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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

ADVERSE REACTIONS: Glaucoma with optic nerve damage, visual acuity and field defects, cataract formation, secondary ocular infection following suppression of host response, and perforation of the globe may occur.

Postmarketing Experience: The following reaction has been identified during post-marketing use of FLAREX® (fluorometholone acetate ophthalmic suspension) in clinical practice. Because reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reaction, which has been chosen for inclusion due to either its seriousness, frequency of reporting, possible causal connection to FLAREX, or a combination of these factors, includes: dysgeusia.

DOSAGE AND ADMINISTRATION: Shake Well Before Using. One to two drops instilled into the conjunctival sac(s) four times daily. During the initial 24 to 48 hours the dosage may be safely increased to two drops every two hours. If no improvement after two weeks, consult physician. Care should be taken not to discontinue therapy prematurely.

HOW SUPPLIED: FLAREX (fluorometholone acetate ophthalmic suspension) is supplied in white low density polyethylene (LDPE) bottles, with natural LDPE dispensing plugs and pink polypropylene closures. The product is supplied as 5mL in an 8 mL bottle.
5 mL: NDC 71776-100-05

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Strings of The Puppet

Musings on life, ophthalmology and the practice of medicine.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

In that sunny place where it only rains at night, and little bunnies frolic in the fields, there exists a physician who makes all their decisions based solely on the needs of the patient—without interference from the government, the insurer or regulatory agencies—free from economic concerns about taking care of their family, paying their staff or saving for retirement. All the years of training provide exactly what our doctor needs to fulfill the Hippocratic oath in its purest sense.

And then you wake up. It's 2 a.m., and you've had another dream. Fortunately, this time, it's about what you imagined medicine would be like when you were young. Very young. Most nights it's an anxiety-filled, panic-ridden rollercoaster of a nightmare where, at every turn, you're boxed in by situations not of your making and impossible to resolve. You pay the bills, code correctly, bill correctly, manage HR, get through an endless clinical day, and still have to deal with paperwork that never ends. Oh, is this not your nightmare? Then perhaps it's the one where some 28-year-old MBA tells you that you need to see 10 more patients a day, or the department chair needs you to take another six weeks of ER call. None of these are what you signed up for, or how you thought you'd spend your career, and yet all are variations on a theme: the loss of control.

I suppose the better question is, "Did we ever have control?" Very few of us get to make all of our own decisions, and make them for all the right reasons, so that the results are better for patient care, better for the physician's mental health and better for our employees and co-workers—as opposed to making the least-worst decisions owing to external forces far beyond our control, like financial, regulatory and corporate factors. And it seems that no matter which model you practice in, it's still the same theme—just with different players, different puppet masters.

Are there perfect options? One would assume that all of us have found our optimized—or perhaps least bad—professional setting. But where we are isn't always where we originally wanted to be. It's scant solace to acknowledge that we likely didn't have complete control of the forces pushing us into our current professional situation. Yet, under our shared constraints, where each of us is can look very different: It runs the gamut from having your name on the building and signing every check to working your 40-hour week with three weeks of vacation. Even though they look different on the surface, there's still that common theme: Our decisions and actions are heavily modified by things we can't control, that rarely have anything to do with patient care. Yet, out of necessity, we make those trade-offs every day as the frustration at having our hands tied continues to mount.

In an ever-more-regulated and resource-scarce environment like health care, we shouldn't be surprised that control flows to those who make the rules and control the money. Yet our obligation to do what's best for our patients remains, and our desire to do what's best for ourselves continues to remain just out of reach. It seems at times that the only options are to either give up, or run to the window, throw it open and yell, "I'm mad as hell and I'm not going to take it anymore!" Neither fixes the problem, nor severs the strings that bind us to a system almost completely out of our control.

Putting aside this depressing conclusion is the sullen acknowledgement that modern life probably couldn't function without each of us ceding at least a degree of control to others—the only question is how much and to whom. And how can we do that and still find our way to that place where it only rains at night? ◀

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

A GOOD CANDIDATE TAKES SKILL TO FIND

Ectasia is to be avoided at all costs, but disease potential may lurk beneath many a cornea. Here are some tips for screening patients successfully.

CHRISTINE LEONARD
ASSOCIATE EDITOR

Refractive screening technology has undergone a number of advances, but weeding out poor candidates in an effort to avoid postoperative ectasia remains a challenge. Gaurav Prakash, MBBS, MD, FRCS (Glasg.), an assistant professor of ophthalmology at the University of Pittsburgh School of Medicine, says the ideal detection method isn't available yet. "Until you have a very evolved clinical sign, it's difficult to predict how a tissue will behave when you do laser," he says. "We're looking at a combination of biomechanical indices and corneal shape."

"If we had a reliable system that could say with certainty that a cornea was normal or abnormal, we could exclude all patients at risk for ectasia and avoid excluding those who have some slightly worrisome findings on examination but are otherwise good candidates," says Edward Manche, MD, a professor of ophthalmology at Stanford University School of Medicine and director of Cornea and Refractive Surgery at the Stanford Eye Laser Center . "As it is, and in my practice, we probably disqualify more patients than actually should be disqualified when we err on the side of caution."

In this article, surgeons discuss ectasia risk and offer strategies for screening and avoiding common pitfalls of data interpretation.

Ectasia Susceptibility

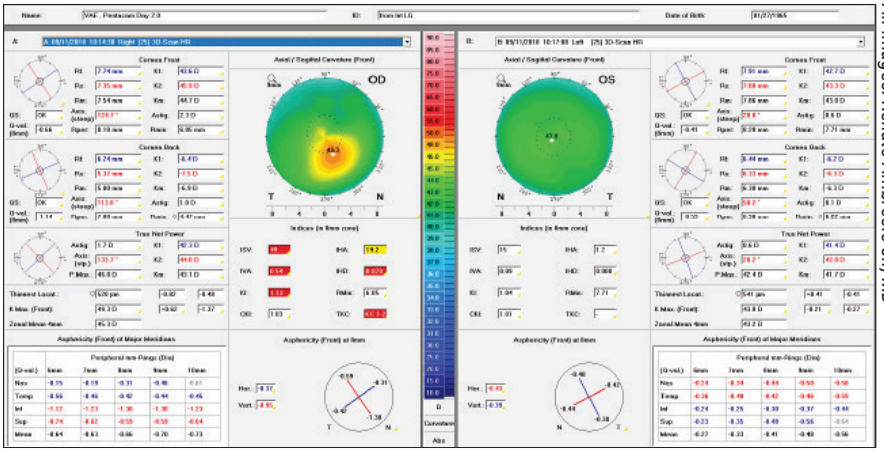
"We've undergone a paradigm shift from detecting mild keratoconus to understanding ectasia susceptibility, which is not the same thing," says Renato Ambrósio Jr., MD, PhD, director of Cornea and Refractive Surgery at the Instituto De Olhos Renato Ambrósio/Visarerio Refracta Personal Laser in Rio De Janeiro and professor of ophthalmology at Federal University of the State of Rio De Janeiro and of São Paulo, Brazil.

He explains that ectasia develops due to biomechanical failure according to innate corneal properties and environmental factors such as laser vision correction and eye rubbing.[1] Even though genetics determines the corneal structure, the environment plays a major role. Biomechanical decompensation begins with focal reduction in elasticity followed by a cycle of increased strain, stress redistribution and focal steepening and thinning.[2]

Some of the modalities in use today for multimodal imaging in refractive screening include Placido disc-based topography, 3D Scheimpflug tomography, segmental tomography with OCT or very high-frequency ultrasound, biomechanical measurements and wavefront analysis. "All of the data from these devices will enhance our ability to characterize ectasia susceptibility and select the best candidates for LVC," says Dr. Ambrósio, who with Michael W. Belin, MD, FACS, co-developed the Belin/Ambrósio enhanced ectasia display, software for early ectasia detection integrated with Pentacam (Oculus), that combines elevation-based and pachymetric corneal evaluation into one display. Dr. Ambrósio believes that artificial intelligence will play a major role in the future of screening, considering the amount of

This article has no commercial sponsorship.

Dr. Manche is a consultant for Avedro/Glaukos and Johnson & Johnson Vision and receives research support from Alcon, Avedro, Zeiss, Presbia, Johnson & Johnson Vision and Novartis. He holds equity in RxSight and Placid0. **Dr. Ambrósio** is a consultant for Alcon/WaveLight, Allergan, Essilor, Genom/União Química, Ofta Vision Health, Mediphacos, Oculus and Zeiss. **Dr. Donnenfeld** is a consultant for Avellino Labs and Glaukos. **Dr. Prakash and Dr. Randleman** have no related financial disclosures.



All images: Renato Ambrósio Jr, MD

Figure 1. Patient is a 53-year-old male interested in refractive surgery who reports gradual vision loss OD. UDVA is 20/60, J3 OD and 20/30, J3 OS. Manifest refraction is -0.75 -2.25 x 25 degrees, giving 20/20-1 OD; and -0.5 -0.75 x 120 degrees, giving 20/15 OS Add. +2.75, J1. He has mild keratoconus in the right eye and normal topography in the left eye.

data generated by such modalities.

"Understanding the impact LVC procedures have on the biomechanical susceptibility of the cornea to progressive ectasia is key," he adds. "A fundamental concept is to accept that any cornea may undergo biomechanical decompensation and ectasia progression."

When assessing a patient's risk for ectasia, J. Bradley Randleman, MD, a professor of ophthalmology at the Cole Eye Institute, Cleveland Clinic, looks at corneal imaging first and then reviews patient-related details, including age and refractive error. He calculates the predicted residual stromal bed thickness (greater than 300 µm is considered low risk and less than 240 µm, high risk) and percent tissue altered, and then re-reviews all available corneal imaging with these patient-related factors in mind.

"I do this because I want to assess the normality of corneal imaging before being swayed by patient factors, and then I want to re-evaluate the imaging within the context of these factors," he says. "The younger the patient, the more concerned I am about any subtle asymmetry in their imaging."

Some patients may still develop ectasia, even when you leave behind sufficient stroma. "In my practice, we generally avoid patients with less than 500 µm of stroma preoperatively," says Dr. Manche. "In those cases, we almost always default to PRK. A thickness of 250 µm is the historically acceptable posterior stromal thickness to leave, but I prefer to leave at least 310 µm so there's room in case I need to do enhancement surgery. If we have to remove more tissue, then I'll consider lens-based surgery or surface ablation with PRK."

"The percentage of tissue altered shouldn't be significantly high," Dr. Prakash adds. "Marcony Santhiago, MD, PhD, proposed this metric for refractive surgery screening in 2014.[3] He found that the percentage of tissue altered, or flap thickness plus ablation depth, divided by preoperative central corneal thickness (= FT + AB =[FT+AB]/CCT), has a strong relationship with ectasia development in eyes with normal topography. It's recommended that a PTA of 40 percent or more be considered for higher-risk patients."

Dr. Randleman's Ectasia Risk Score System was built based on subjective placido-based curvature analysis and patient-related factors. The ERSS takes into account topography pattern, residual stromal bed thickness, age, corneal thickness and manifest refraction to produce a risk score ranging from zero to four, with higher scores indicating greater risk.

"I still utilize all of the factors that went into the ERSS, at least conceptually, but I now have additional data available that I use for all screenings," Dr. Randleman says. "I find regional pachymetry maps to be particularly useful and better than single-point thickness metrics. I also find elevation maps to be complimentary to curvature maps. If, for instance, there's a major focal curvature change but nothing on anterior elevation, then I look closely to see if there's some corneal process causing this finding, such as EBMD or another scarring process. I do review the posterior elevation maps as well, but I've found these to be less predictive for risk than anterior curvature and elevation."

"Dr. Randleman has done remarkable work on understanding ectasia," Dr. Ambrósio says. "He's commended to be the first to integrate different parameters for evaluating ectasia risk. A very important contribution from his scale was age. Age is a surrogate for corneal biomechanical properties. We have many studies *in vitro* and *in vivo* demonstrating this. However, my major concern with his scale is that he uses forme fruste keratoconus as a topographic criterion. FFKC is an abortive form of keratoconus that may or may not progress to the full-blown clinical condition. While the 2015 Global consensus shows no agreement on the definition of FFKC, there was consensus that keratoconus is bilateral, and that ectasia may occur unilaterally due to biomechanical stress.

"I'd define FFKC as a cornea with high ectasia susceptibility," he continues. "These eyes have normal topography, but the fellow eye has clinical ectasia. However, we must recognize that some of these very asymmetric cases are indeed unilateral (not keratoconus) ectasia cases. Ultimately, I agree that FFKC is the most important risk factor for developing progressive ectasia after

LVC; the problem is how to define and how to identify FFKC.[4] Topography enhances the sensitivity of detecting abnormalities in patients with good distance-corrected vision and normal biomicroscopy, but often it's not enough to pick up subclinical disease. We need to go beyond, not over, front surface curvature. This means adding more data from diagnostic tests, such as tomographic and biomechanical data."

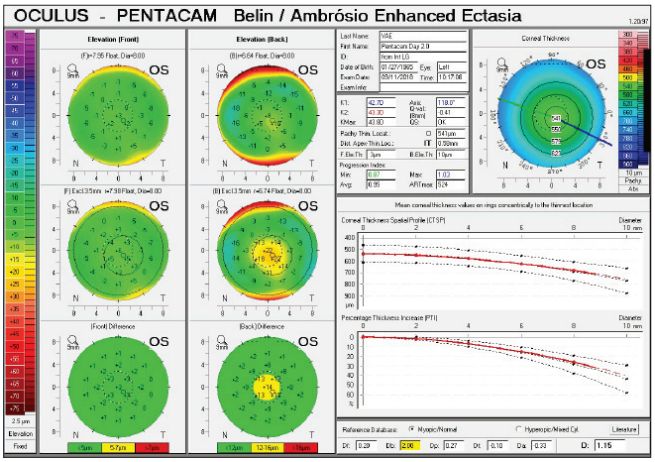


Figure 2. An elevation and pachymetric assessment (Belin/Ambrósio Enhanced Ectasia Display) of the left eye of the same patient from Figure 1, showing mild elevation change and borderline tomography. Elevation maps are viewed by comparing the data to a standard reference surface. Physicians say that raw elevation data on its own doesn't have enough surface variability for a clinician to easily distinguish normal from abnormal corneas on qualitative inspection. Subtracting a reference surface exaggerates the differences.[8]

Biomechanical Challenges

Biomechanical properties of the cornea aren't easy to analyze. "We've done work with different non-contact tonometers," Dr. Ambrósio says. "Our work on biomechanical assessment started in 2003 with a prototype of ORA (Reichert), which documents corneal deformation caused by an air puff with a single-point reflex. This work demonstrated the clinical relevance of such measures for ectasia detection. A few years later, we collaborated on the development of the Corvis Scheimpflug technology (Oculus). The Corvis ST provides an 8-mm Scheimpflug image so you can see corneal deformation in more detail. In addition, Corvis ST and Pentacam are from the same company, so the generated information can be integrated through artificial intelligence algorithms, such as the Ambrósio, Roberts and Vinciguerra (ARV) Display (*Figure 3*).[5]

"One of the biggest problems with biomechanics currently is that we have a large range of normal," says Dr. Prakash. "When you have a large distribution of biomechanical properties, affected by corneal thickness, genetics and ethnicity, it's difficult to define what's normal and abnormal, especially in subtle cases right on the decision boundary.

"It'll be interesting to see if in future there will be robust and more universal criteria that combine biomechanics with tomography on multiple devices," he continues. "As of now, if you have keratoconus, the biomechanics will be altered and the cornea will have different indices compared to normal, but we're still looking for variation."

Brillouin Microscopy

An emerging technology for analyzing corneal biomechanics is Brillouin optical microscopy, a type of optical elastography that uses low-power, near-infrared laser to determine mechanical compressibility of tissue by analyzing the return signal spectrum with confocal spectrometry.[6] "Brillouin microscopy is a fascinating technology that has great potential," says Dr. Randleman. "We're starting our trials to measure patients before and after laser vision correction (PRK, LASIK and SMILE) to see what differences we're able to detect in their corneas regionally. We're also evaluating patients with different states of keratoconus to see how these eyes differ from normal corneas.

"The Brillouin technique is non-invasive, so it can be repeated multiple times as needed, and it's the first technology that can provide a picture of what's occurring focally, both in terms of location on the cornea and also with respect to depth within the cornea," he continues. "This means we can detect where in the cornea the differences are occurring. This capability is different from those of Corvis or the ORA, which can only provide a global sense of corneal stiffness, and both require an air puff impulse that can generate variable responses in patients.

"Brillouin is still in the early research phases," he notes, "but it could become a major part of preoperative evaluation and procedure selection based on the combination of the patient's individual biomechanical profile and the relative impact of different LVC options."

In the meantime, Dr. Manche says he screens all potential refractive surgery patients using wavefront aberrometry, in addition to topography and tomography. "We're using the iDesign 2.0 (Johnson & Johnson Vision), which has been available since 2018," he says. "It has five integrated measurements including wavefront aberrometry, wavefront refraction, full-gradient corneal topography, keratometry and pupillometry. We also perform pachymetry, both optical and ultrasonic, when screening patients."

Epithelial Mapping

Dr. Randleman says a useful technology that's arisen over the past decade is epithelial thickness mapping in the form of either very high-frequency digital ultrasound (VHFDU), or optical coherence tomography. "In our practice we use OCT-based total and epithelial thickness maps for all of our refractive screenings, and I find this data to be remarkably useful," he says. "The pioneering work by Dan Reinstein, MD, on epithelial remodeling (using VHFDU) and then the development of this mapping capability using OCT by David Huang, MD,

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REENVISION DRY EYE

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References: 1. Brazzell RK, Zickl L, Farrelly J, et al. Prevalence and characteristics of dry eye flares: a patient questionnaire survey. Presented at: AAO 2019: October 12-15, 2019; San Francisco, CA. **2.** Brazzell RK, Zickl L, Farrelly J, et al. Prevalence and characteristics of symptomatic dry eye flares: results from patient questionnaire surveys. Poster presented at: AAOPT 2019: October 23-27, 2019; Orlando, FL. **3.** 2020 Study of Dry Eye Sufferers. Conducted by Multi-sponsor Surveys, Inc.

PhD, has revolutionized our understanding of early, subtle changes that can clarify borderline screening patients.

"As an example, if there's focal steepening on anterior curvature imaging that coincides with epithelial thinning, that's a red flag for me, and I avoid surgery in those cases," he notes. "Alternatively, if focal steepening is accompanied by focal epithelial hypertrophy, I have less concern and often will offer patients with those findings corneal refractive surgery.

"The normal cornea has low thickness variation across the center, but also tends to exhibit mild inferior hypertrophy," he says. "Focal thinning isn't typical, and if this finding is seen in conjunction with corneal steepening, this is particularly concerning. Alternatively, focal steepening coincident with focal epithelial hypertrophy is a comforting finding."

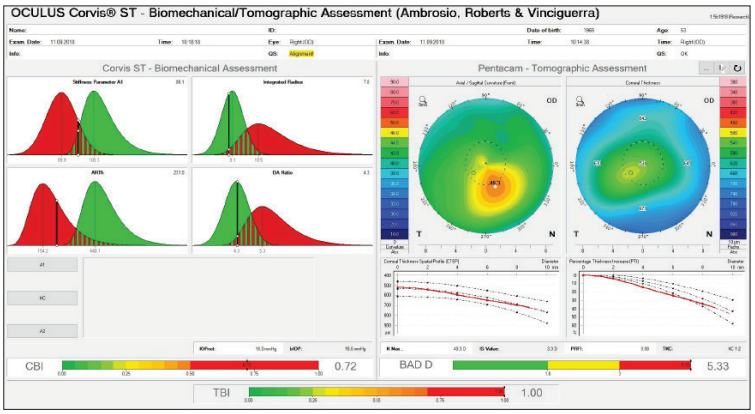

Figure 3. A biomechanical/tomographic assessment (Ambrósio, Roberts & Vinciguerra Display) of the same patient's right eye from Figures 1 and 2, showing abnormal tomography and biomechanics.

Strategies for Success

Avoiding patients who are likely to develop postoperative ectasia is key, but it's not always easy to identify them, especially in borderline cases. Here are some strategies for sharpening your screening process:

• ***Look at as many scans as possible to hone your interpretive skills.*** "The best way to get through the learning curve of understanding topography and tomography is to see as many scans as possible," says Dr. Prakash. "When you're working in a single surgery practice or a small practice, this might be difficult, so I ask people to look at resources such as *JCRS*, clinical cases, sessions or online repositories of topography. Try to assess why the topography is normal or abnormal. It's all about repetition."

• ***Don't compare data from two different devices directly.*** A large part of diagnostic data interpretation comes down to knowing how to use a specific device and how to understand and compare the outcomes of that device, says Dr. Prakash. "Say you use Pentacam, and a patient comes to you with scans taken with the Cirrus (Zeiss) or the Atlas (Zeiss)," he says. "It's been clinically proven that you can't compare the data directly between two different devices. You have to either have the conversions in your head or redo the scans. This is especially important when looking at borderline scans."

• ***Stay alert for off-center corneal thinning on pachymetry.*** "The normal cornea is thinnest centrally and has a relatively predictable progression of thickening towards the periphery," Dr. Randleman explains. "If the thinnest point is significantly deviated from the center, and/or if there's minimal thickness progression towards the periphery, these are both concerning findings."

• ***Pay attention to the scale when interpreting topographic maps.*** "Evaluating corneal front surface topography maps is subjective," says Dr. Ambrósio. "The first thing you should do when evaluating a topography map, or any kind of map, is to look at the scale bar. Changing the scale may completely change your subjective interpretation. Try to standardize the scales and parameters you use."

• ***Be aware of your subjective interpretation.*** It's important for clinicians to be as objective as possible when interpreting scans and data, to compensate for the inherently subjective nature of topographic data interpretation. Dr. Ambrósio advises a thorough understanding of the rationale for statistical analysis, sensitivity, specificity and accuracy, when comparing variables and picking the best parameters.

He notes that understanding how certain maps are constructed—such as curvature maps, which are divided into axial and tangential maps, each with their unique sensitivities and detection strengths—will also alert you to possible errors in subjective classification. "Be sure you know which map you're looking at," he says. "A tangential map is highly sensitive because it's aim is to identify abnormalities, but this also means it's noisier than an axial map."

He and his colleagues, including Dr. Randleman, conducted a study on the subjective variability of classification. "We had 11 experts classifying 25 preoperative axial curvature maps using the Ectasia Risk Scoring System," he says. "First, they reviewed each case represented with an absolute scale; three months later they reviewed the same cases with a normative scale, both times masked to the patient group. Interestingly, eight out of 11 experts (73 percent) reported statistically higher scores when using the normative scale. The level of variability was more than 60 percent." Of all 550 topographic analyses, the same classification of the two scales was reported in 121 case pairs (44 percent).[7]

• ***Don't rely solely on algorithms and metrics.*** Many corneal imaging devices have AI analysis built in which can assign a score based on the percentage of agreement with keratoconus, notes Dr. Manche. He says this

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- Use Upneeq with caution in patients with cerebral or coronary insufficiency or Sjögren's syndrome. Advise patients to seek medical care if signs and symptoms of potentiation of vascular insufficiency develop.
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ADVERSE REACTIONS

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DRUG INTERACTIONS

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- Caution is advised in patients taking monoamine oxidase inhibitors which can affect the metabolism and uptake of circulating amines.

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Please see next page for Brief Summary of full Prescribing Information.

Reference: 1. Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1%. [Prescribing Information].

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Bridgewater, NJ 08807
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BRIEF SUMMARY: The following is a brief summary only; see full Prescribing Information at https://www.upneeq.com/Upneeq-PI.pdf for complete information.

1 INDICATIONS AND USAGE

UPNEEQ is indicated for the treatment of acquired blepharoptosis in adults.

2 DOSAGE AND ADMINISTRATION

Contact lenses should be removed prior to instillation of UPNEEQ and may be reinserted 15 minutes following its administration.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least 15 minutes between applications.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Potential Impacts on Cardiovascular Disease

Alpha-adrenergic agonists may impact blood pressure. UPNEEQ should be used with caution in patients with severe or unstable cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

5.2 Potentiation of Vascular Insufficiency

UPNEEQ should be used with caution in patients with cerebral or coronary insufficiency, or Sjögren's syndrome. Advise patients to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop.

5.3 Risk of Angle Closure Glaucoma

UPNEEQ may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop.

5.4 Risk of Contamination

Patients should not touch the tip of the single patient-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

6 ADVERSE REACTIONS

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 the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 360 subjects with acquired blepharoptosis were treated with UPNEEQ once daily in each eye for at least 6 weeks in three controlled Phase 3 clinical trials, including 203 subjects treated with UPNEEQ for 6 weeks and 157 subjects treated with UPNEEQ for 12 weeks. Adverse reactions that occurred in 1-5% of subjects treated with UPNEEQ were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation, and headache.

7 DRUG INTERACTIONS

7.1 Anti-hypertensives/Cardiac Glycosides

Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives, and/or cardiac glycosides is advised.

Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.

7.2 Monoamine Oxidase Inhibitors

Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on UPNEEQ use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 7 and 278 times the maximum recommended human ophthalmic dose (MRHOD), respectively, based on dose comparison. [see Data]. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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

Effects on embryo-fetal development were evaluated in rats and rabbits following oral administration of oxymetazoline hydrochloride during the period of organogenesis. Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 0.2 mg/kg/day in pregnant rats during the period of organogenesis (28 times the MRHOD, on a dose comparison basis). Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 1 mg/kg/day in pregnant rabbits during the period of organogenesis (278 times the MRHOD, on a dose comparison basis). Maternal toxicity, including decreased maternal body weight, was produced at the high dose of 1 mg/kg/day in pregnant rabbits and was associated with findings of delayed skeletal ossification.

In a rat prenatal and postnatal development study, oxymetazoline hydrochloride was orally administered to pregnant rats once daily from gestation day 6 through lactation day 20. Maternal toxicity was produced at the high dose of 0.2 mg/kg/day (28 times the MRHOD, on a dose comparison basis) in pregnant rats and was associated with an increase in pup mortality and reduced pup body weights. Delayed sexual maturation was noted at 0.1 mg/kg/day (14 times the MRHOD, on a dose comparison basis). Oxymetazoline hydrochloride did not have any adverse effects on fetal development at a dose of 0.05 mg/kg/day (7 times the MRHOD, on a dose comparison basis).

8.2 Lactation

Risk Summary

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breast milk production, or to establish the level of oxymetazoline present in human breast milk post-dose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for UPNEEQ and any potential adverse effects on the breastfed child from UPNEEQ.

8.4 Pediatric Use

Safety and effectiveness of UPNEEQ have not been established in pediatric patients under 13 years of age.

8.5 Geriatric Use

Three hundred and fifteen subjects aged 65 years and older received treatment with UPNEEQ (n = 216) or vehicle (n = 99) in clinical trials. No overall differences in safety or effectiveness were observed between subjects 65 years of age and older and younger subjects.

10 OVERDOSAGE

Accidental oral ingestion of topical intended solutions (including ophthalmic solutions and nasal sprays) containing imidazoline derivatives (e.g., oxymetazoline) in children has resulted in serious adverse events requiring hospitalization, including nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and coma. Keep UPNEEQ out of reach of children.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

RVL PHARMACEUTICALS, INC.

Manufactured for: RVL Pharmaceuticals, Inc.
Bridgewater, New Jersey 08807

PM-US-UPN-0203 01/21

can be very helpful for clinicians just starting out, but adds that "it's always good to confirm the AI analysis with other diagnostic testing."

Likewise, Dr. Ambrosio says that though objective data such as that from the Belin/Ambrósio display are invaluable when evaluating a patient, they're not replacements for physicians' cognition. "You can make clinical judgments based on these data, but don't let the data dictate what you do," he advises. "Understand the limitations of your diagnostic tools and what you're trying to achieve with the data."

"Screening metrics are attractive because they take a number of factors and reduce them to a single value," Dr. Randleman says. "Unfortunately, the attractiveness of metrics doesn't always convey their underlying value or shortcomings. Regarding the Belin/Ambrosio display, I haven't found any of the available metrics to be particularly clarifying in screening, and unfortunately they can be misleading. I have, for instance, reviewed a number of cases that unfortunately developed ectasia after LASIK where none of the metrics on the enhanced ectasia display were reported as abnormal. I caution everyone to review any specific screening metrics but not rely upon them more than careful interpretation of the raw data, because no specific metrics have been shown to be more accurate than this approach at this time."

Artifacts

Artifacts will skew your results. "Your interpretation is as good as the data you get," says Dr. Prakash. "We use the phrase: "Garbage in, garbage out." Here are some artifacts to watch out for:

• ***Moving and alignment artifacts.*** Today's devices are much faster than their predecessors, taking about 15 to 20 seconds to complete a scan, but even so—if a patient isn't able to sit still for the scan, that movement may affect the scan quality. "Not looking straight at the light, blinking too much and improper head alignment can also cause artifacts," Dr. Prakash says. "I always recommend physicians look at the scan and the eye together. Don't treat the scan, treat the eye. And don't be afraid to redo a scan if it's not good quality."

• ***A suboptimal ocular surface.*** Dr. Prakash says that dry eye can result in false positives such as the appearance of steeper or flatter areas of the cornea that don't actually exist. "Scars can also change how the cornea looks, so keep that in mind when looking at your scans," he adds.

"A good slit lamp examination of the lids and lashes as well as the ocular surface, including tear-film breakup time and corneal staining with vital dyes such as fluorescein and lissamine green, will help you rule out patients with dry eye," Dr. Manche says. "Look for MGD, blepharitis and inflammation."

• ***Contact lens wear.*** Previous contact lens wear can cause the cornea to look more regular or irregular than it truly is, so ensure your patient has discontinued wearing their contacts for a period of time before performing any scans: about one week for soft contact lenses and two weeks for toric lenses. For rigid gas-permeable lenses, one month of discontinuation per decade of wear is the rule of thumb, according to experts. "This is especially important for a long-term ortho-K wearer, since those lenses flatten the cornea," Dr. Manche says. "You need to follow those patients for a fairly long period of time with serial corneal topographies to ensure the induced flattening has resolved."

The Final Frontier: Genetic Screening

"Keratoconus is multifactorial and caused by multiple genes, so it's not easy to detect," says Dr. Manche. "However, there's a new genetic test for keratoconus out now from Avellino Labs." (AvaGen was released in the U.S. in June 2021.)

Eric Donnenfeld, MD, a clinical professor of ophthalmology at New York University Medical Center, partner at Ophthalmic Consultants of Long Island and consultant for Avellino Labs, says this is the first DNA test available for keratoconus. "There are about 50 different genes involved in the development of keratoconus," he says. "The test examines 75 keratoconus-related genes with more than 2,000 variants and stratifies the risk of developing keratoconus over a lifetime based on individual genes and on the combination of genes a patient has. It can also diagnose other corneal dystrophies such as granular, lattice, Reis-Bucklers and Theill-Behnke dystrophies."

He says he's just added this genetic test to his office's armamentarium. "If I see mildly abnormal topography, having a stratified risk score reflecting a patient's chance of developing keratoconus makes me much more comfortable in my decision as to whether they should have LASIK or PRK or just be followed. I also use this test for patients who have family members with keratoconus and for children of parents with keratoconus. The key to eradicating keratoconus is diagnosing it as early as possible, so patients can have cross-linking performed at a younger age." ◀

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INCREASING PREMIUM IOLS (AND SERVICE)

More surgeons are expanding in the lucrative and increasingly efficacious field of refractive cataract surgery. Where do you fit in?

SEAN MCKINNEY
SENIOR EDITOR

How has the cataract surgery landscape changed since premium IOLs were introduced 35 years ago? And how has the landscape changed since the femtosecond laser debuted in 2009? Most important: How have you and other ophthalmologists responded? "These days, the short answer to all three of those questions is very quickly," says Michael Greenwood, MD, a cataract and refractive surgeon who also specializes in glaucoma and cornea at Vance Thompson Vision in Fargo, North Dakota. "We're used to seeing new technologies come along every few years, but now it seems like it's almost monthly. The outcomes are getting better and better. Surgeons are growing more comfortable with the newest technology, and, as a result, patients are benefiting from an explosion of innovations."

Other surgeons report similar impressions. In this article, the ones who are increasing their success with premium cataract surgery explain how they incorporate new IOLs into their practices, identify ideal surgical candidates, promote the refractive benefits of surgery, organize staff around new team approaches to screening and presentation and use femtosecond laser technology to master the best techniques. The surgeons also offer advice to get you started on the path to similar success.

Recent Rapid Evolution

Dr. Greenwood says the premium IOL market really started to gain momentum with the introduction of low-add multifocals several years ago, even though haloes and glare were still issues. "Now we're in the era of trifocality and extended-depth-of-focus, and that has allowed even better distance and near vision and even better intermediate vision, which had been the least-beneficial feature of past premium lenses," he says. "Along with the functional improvements found in trifocals and EDOFs, the dysphotopsia profiles have gotten even better. So now surgeons and patients can have a lot of confidence, knowing that outcomes are going to be good. And the trade-offs found in the dysphotopsia profile will be very mild compared to the benefits patients will get from the presbyopia-correcting lenses."

Dr. Greenwood says his practice used to have 35 to 40 percent of patients choosing some kind of premium option to minimize their dependence on glasses. "But as we come out of COVID, the numbers have crept up a little bit. And that's probably because of patients' ability to prioritize their vision a little bit more," he says. "Patients may have more money available because of less vacation time. A variety of factors have come into play."

Ideal Candidates = Success

When earlier generations of premium IOLs first became available many years ago, the surgeons at Eye Centers of Tennessee began to implant thousands of the new lenses, believing a new day in surgical excellence and outcomes had arrived. But a troubling trend soon followed.

This article has no commercial sponsorship.

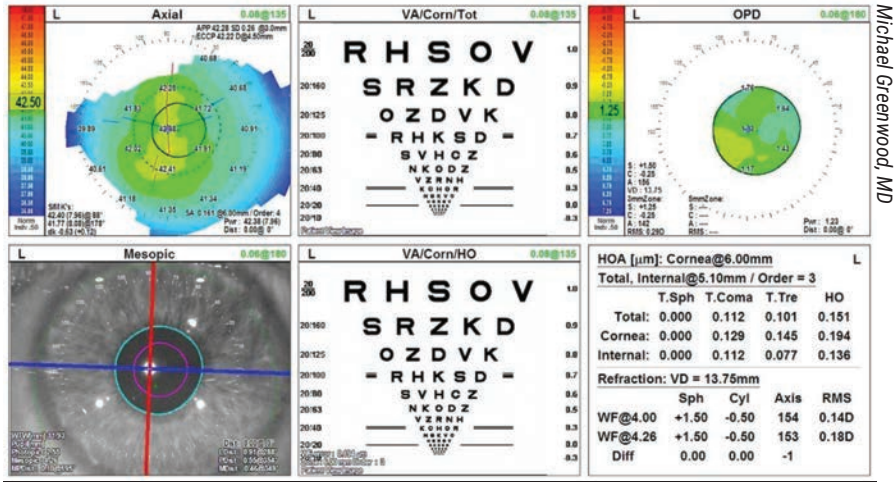
Dr. Aker is a speaker for Johnson & Johnson Vision and Bausch + Lomb. He also serves as Medical Monitor for the CORD Group. **Dr. Patterson** is a consultant for Carl Zeiss Meditech, Bausch + Lomb and Johnson & Johnson Vision. **Dr. Greenwood** is a speaker for Alcon. **Dr. Wallace** reports no financial relationships with companies that make products mentioned in this article.

"More and more patients came back, and they weren't very thrilled with their vision," says Michael Patterson, DO, a comprehensive ophthalmologist at the practice. "The surgeons in our practice couldn't figure out why this was happening, because the patients could see 20/20 on the eye chart. Since then, though, we've learned they weren't happy because they hadn't been good candidates. We learned more about dry eye, high angle kappa, and other challenges to optimal postop vision that hadn't entered our thinking before."

Currently, he says, the practice has adopted ever-advancing diagnostic technologies that have enabled surgeons to confidently tell patients if they're good candidates for an increasingly sophisticated array of premium IOL technologies which, like the lenses, have grown more sharply focused on inclusion and exclusion criteria.

"Now that we can more accurately predict good candidates and identify patients who aren't good candidates, we've achieved a much higher satisfaction ratio with premium IOLs than we had in the past," says Dr. Patterson. "Whether it be from us using OCT on the retina, corneal topography on every single patient who's getting a premium lens, or other tests, we can now tell patients, definitively, that they're great candidates for particular lenses. We can almost guarantee that they'll see 20/20, but, most importantly, that they'll be satisfied with their vision before we do the surgery.

"This is certainly a game-changer in ophthalmology because, previously, the message was, 'We're going to get you seeing the best we can,'" he continues. "This has helped with our chair time in the clinic, too, and it also helps postoperatively. Our assistants and coordinators know they're not going to have to spend a lot of time with unpleasant surprises and unhappy patients. If we've identified patients as ideal premium lens patients preoperatively, we don't need to have these difficult conversations. That's a huge advantage in the use of premium lenses today."



Michael Greenwood, MD

Figure 1. A NIDEK OPD III image provides various data, but surgeons say one of the most important points when considering a patient for premium IOLs is the "total cornea HOA," or higher-order aberrations measurement, which helps to determine if a patient would be a good multifocal IOL candidate.

Dr. Patterson notes that the other important part of this growing success story is the evolution of the IOLs. "The newest IOL technologies, primarily from Johnson & Johnson Vision and Alcon, have enhanced lenses to the point where glare and halos haven't been as significant a problem during the past two to three years," Dr. Patterson continues. "For example, in the Alcon lens, the company increased the center button to put more distance vision through that area. The reason that helps is because it causes fewer halos and less glare in the company's ActiveFocus IOL. The Johnson & Johnson Symfony offers a similar process. And now J&J has just launched the Tecnis Synergy lens, while Alcon had previously launched PanOptix [and recently launched the Vivity]. These combinations have given patients better choices for improved vision, with a greater range."

Refractive Cataract Strategies

Dr. Patterson says his practice embraces refractive cataract surgery to meet two needs:

- patients' desire to wear no distance glasses, enabling them to drive without them, guaranteed; or
- patients' desire to not wear glasses for distance and near.

"Our refractive cataract volume has grown 10 percent to about 35 percent of 4,000 cataract surgeries per year," he says of the 10 locations at Eye Centers of Tennessee. "That's high for us because many patients around here don't have a lot of extra money to spend. We've been able to achieve this because we have so much confidence in the premium technologies we have today. We can totally guarantee what we say we're going to do."

Optimism is somewhat guarded at some practices, however. Alan Aker, MD, who owns and operates Aker Kasten Eye Center with his wife, Ann Kasten, MD, in Boca Raton, Florida, remains mindful of how the sometimes over-promised and under-delivered performance of yesteryear's premium IOLs has affected surgeons' reputations and patient confidence.

"We had a number of factors working against us in the past," he

WHAT ANATOMIC RESULTS COULD HE SEE THIS YEAR?

Of 134 patients treated in a DR clinical trial

80% SAW A ≥2-STEP DRSS IMPROVEMENT[1]

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DR.

PANORAMA study design: Multicenter, double-masked, controlled clinical study in which patients with moderately severe to severe NPDR (ETDRS-DRSS: 47 or 53) without CI-DME (N=402; age range: 25-85 years, with a mean of 56 years) were randomized to receive 1 of 2 EYLEA dosing regimens or sham. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). During Year 2 (Weeks 52-96), patients randomized to one of the EYLEA arms received a different dosing regimen.[1]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

STARTING EYLEA EARLIER MAY HELP PREVENT DR PROGRESSION

Primary Endpoint (Year 1)		Secondary Endpoint (Year 1)	
Proportion of patients with a ≥2-step DRSS improvement[1,2,*]		Reduction in the risk of developing PDR or ASNV or CI-DME[2,*,†]	
EYLEA Q8 (n=134)	EYLEA Q16 (n=135)	EYLEA Q8 (n=134)	EYLEA Q16 (n=135)
80% vs 15% in the sham group (n=133)	**65%** vs 15% in the sham group (n=133)	**79%** **Risk Reduction** **Event rate:** 11% vs 42% in the sham group (n=133)	**82%** **Risk Reduction** **Event rate:** 10% vs 42% in the sham group (n=133)

P<0.01 vs sham.

- The recommended dose for EYLEA in DR is 2 mg (0.05 mL) administered by intravitreal injection Q4 (≈every 28 days, monthly) for the first 5 injections, followed by 2 mg Q8 (every 2 months)[1]
- Although EYLEA may be dosed as frequently as 2 mg Q4 (≈every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed Q4 compared with Q8. Some patients may need Q4 (monthly) dosing after the first 20 weeks (5 months)[1]

*Full analysis set.
†Event rate was estimated using the Kaplan-Meier method. Composite endpoint of developing PDR, ASNV was diagnosed by either the reading center or investigator.

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

anti-VEGF; anti–vascular endothelial growth factor; ASNV, anterior segment neovascularization; CI-DME, central-involved Diabetic Macular Edema; ETDRS-DRSS, Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale; PDR, proliferative diabetic retinopathy; Q4, every 4 weeks; Q8, every 8 weeks; Q16, every 16 weeks.

WARNINGS AND PRECAUTIONS (continued)

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

ADVERSE REACTIONS

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

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Wykoff CC. Intravitreal aflibercept for moderately severe to severe non-proliferative diabetic retinopathy (NPDR): 2-year outcomes of the phase 3 PANORAMA study. Data presented at: Angiogenesis, Exudation, and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

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

03/2021
EYL.21.02.0049

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

REGENERON

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Tarrytown, NY 10591

Issue Date: 08/2019
Initial U.S. Approval: 2011

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

EYL.20.09.0052

says. "The patients who received those lenses couldn't drive at night, and doctors stopped implanting them because of these issues. Many surgeons didn't know, or didn't want to know, how to replace the lenses. And that remains a big issue. When you put in a lens, you have to know how to take it out to replace it with a lens that satisfies an unhappy patient."

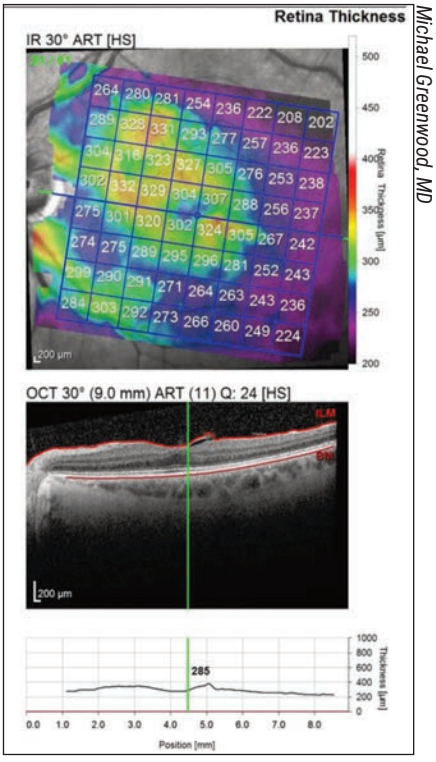
The newer IOLs, he acknowledges, have significantly changed the dynamics in the marketplace. "We can put in lenses without trepidation over the potential for more disappointments," he says. "All the lenses that are currently available have advantages and disadvantages, but we've definitely seen improvements."

Dr. Aker's enthusiasm for today's premium IOLs has translated into a conversion rate of more than 70 percent of his practice's 2,500 cataract surgery patients per year into premium lens patients. However, he emphasizes that premium lenses aren't for every patient.

"You have to manage expectations," he notes. "I tell patients that there's no perfect lens, and there may never be."

He urges colleagues to be aware of potential variations in outcomes among patients, sometimes for reasons that don't seem discernible. "Some patients get extraordinary results," he observes. "They can read like a champ and see distance like a hawk," typically in IOLs not designed for near vision correction.

"These outcomes are great, of course, but you have to watch for word-of-mouth success stories that can create unrealistic expectations among patients referred to you by their extremely happy friends," he continues. "We tell patients, 'You may have heard of some patients that have done really well with reading with these lenses. If you get that, consider it a bonus, because the lens doesn't normally perform that way.'



Michael Greenwood, MD

Figure 2. This macular OCT scan shows loss of foveal depression following an epiretinal membrane peel. Surgeons say the loss of foveal depression tells this surgeon his patient isn't an ideal multifocal IOL candidate.

We try to stay ever mindful of the lessons we learned not so long ago. You always want to under-promise and over-deliver."

R. Bruce Wallace III, MD, FACS, founder and medical director of Wallace Eye Surgery in Alexandria, Louisiana, and clinical professor of ophthalmology at Louisiana State University and Tulane Schools of Medicine in New Orleans, says major improvements in the refractive benefits of today's lens-based surgery have led to much more patient satisfaction, even with standard monofocal IOLs. "Today's surgeon now has better tools to take the refractive benefits to the next level by allowing more dependable reduction in spectacle dependency for distance and near vision," he notes. "We've learned that, with clinic teamwork and effective preoperative patient counseling, successful postoperative outcomes can be achieved."

It Takes a Team

In the old days, surgeons say, the complex challenge of explaining various IOL options was often left to the surgeon, one-on-one with the patient. Leaders of the most successful premium practices today ask all employees of the practice to share in this core responsibility. That means everyone from the front desk staff to the business staff to the techs in the back office. Some surgeons have designated specialists who dedicate most or all of their time to educating and screening patients for premium IOLs.

"We look for severe dry eyes," says Megan Flatt, COA, Dr. Patterson's executive surgical assistant at the Eye Centers of Tennessee. "We don't want to add to those problems with surgery, especially with premium IOLs. We explain to potential surgical candidates that the cornea is their front window that they're looking through. So if they have a disruption on the cornea, they're not going to see clearly, even with a premium technology lens. Even if it's perfectly centered in the bag, their quality of vision is still not going to be optimal because of a cornea that's not. Sometimes you need to spend a little time with them to get these ideas across. Some other factors that we rule out are any retinal problems, any glaucoma, or high angle kappa and alpha issues.

"We do have patients who still want to have the technology," she continues. "But we set the expectations with the patients. 'Hey, listen,' I'll tell them. 'You're not a perfect candidate for this option. But if you still want that technology, we may need to change the lens we're using for the surgery. You're not going to see perfectly at some ranges because it doesn't provide the perfect near qualities that you'd like to have, for example. But we can give you a lens

that reduces the chance of glare and halos."

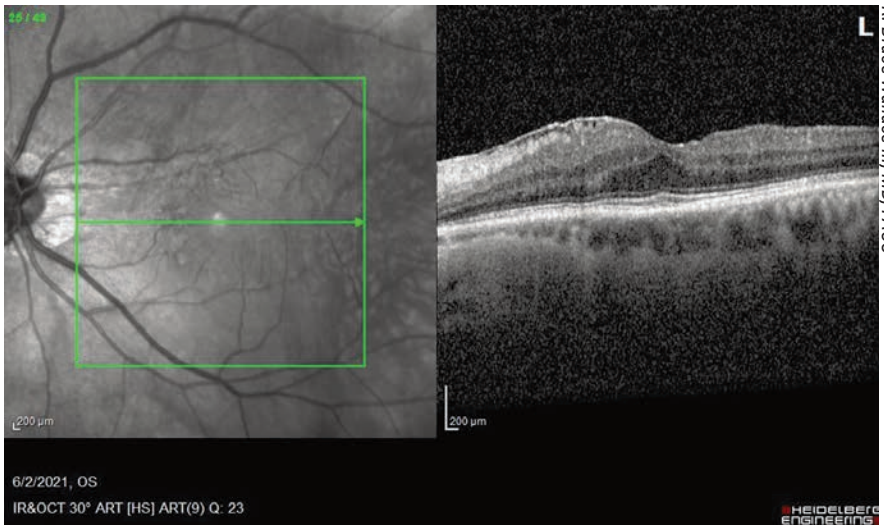
Dr. Wallace relies on similar support in his practice. "If you don't use a team approach for a refractive cataract practice, it doesn't work so well," he says. "Most significantly, the team members need to know how important they are in this effort. If they're not integral to the success of this whole system, then they're not going to give you what they can give you in terms of quality of care for the patients, and they aren't going to enjoy what they do, which is very important as well. It's critical that they be educated."

Bill Wallace, MBA, Dr. Wallace's son and the practice administrator, carries the same message throughout the office and into the practice's ambulatory surgery center.

"I recently delivered a spotlight talk on refractive cataract surgery to the staff," Mr. Wallace says. "One of the measures of success is the enthusiasm we see in our employees. They want to know more about the options that are available, and they're always asking for additional presentations to make sure they're up to date. To see this staff so hungry for the information they need to make sure we're successful is a clear indicator that we're doing things right. We have patients who come in for multiple visits before deciding on their surgery. This isn't a decision that's made during one visit. It speaks to the notion that this is a once-in-a-lifetime opportunity."

Robert Crotty, OD, a doctor at the practice, whose office desk sits across from Dr. Wallace's, also plays a key role in evaluating, educating, screening, following up and caring for cataract surgery patients. He even lectures at state optometry meetings to teach ODs how to help drive the success of a refractive cataract surgery practice.

"The newer lenses have opened up the door to allow these patients to become candidates for premium service," says Dr. Crotty. "However, screening these patients is very important. Just this morning, we caught an epiretinal membrane when screening for a patient's preferred type of lens. That pathology obviously limited the kind of lens choice we would recommend. Had it not been for that screening, this patient could have become one of those patients who could've ended up unhappy." (*See Figure 3 above.*)



R. Bruce Wallace III, MD, FACS

Figure 3. Preop macular OCT reveals an epiretinal membrane that wasn't detected during a preop retinal exam. The pathology, limiting the patient's premium IOL choices, could have led to an unhappy postop patient, had it not been for this advanced screening, which surgeons say they're using more frequently to root out potential problem cases.

Dr. Crotty places equal importance on patient education. "The more patients learn, whether it's from the staff or the doctors, there's always more to tell them to clarify, confirm and expand on their knowledge base. By giving patients this information, they know that we're providing them with the best opportunity to make a once-in-a-lifetime decision to seek the best care they can get for their eyes. When we see a patient who's delighted with his or her surgical result, that's what really gets us excited. That's what we call 'sharing the value.'"

To support his efforts, Dr. Greenwood says he and his fellow surgeons rely on what he describes as five or six "touch points" to educate and advise patients on today's complex IOL offerings. "One touch point can come from the referring optometrists, although that's not expected," he says. "Another touch point comes when we send patients something in the mail, whether it's a mail offer or a mail/text video that they can view. Another touch point is what we put on our website. When patients visit our office and communicate with staff while they get testing done, that's another touch point.

"When the doctors visit with the patients, that's another touch point," Dr. Greenwood continues. "And while the doctors are finishing everything up regarding the discussion, and the patients are making their decisions, that's just another touch point and an additional time for education. I'd estimate that 95 percent of our patients make the decision on how they want to proceed during that first visit. But again, we've done a lot of education on the front end, so these are informed decisions."

Increasing Team Skills

Some practices are creating unique positions to help develop their premium practices. For example, at the Aker Kasten Eye Center, Jeffrey Rapp, who has a PhD in human physiology, serves as director of

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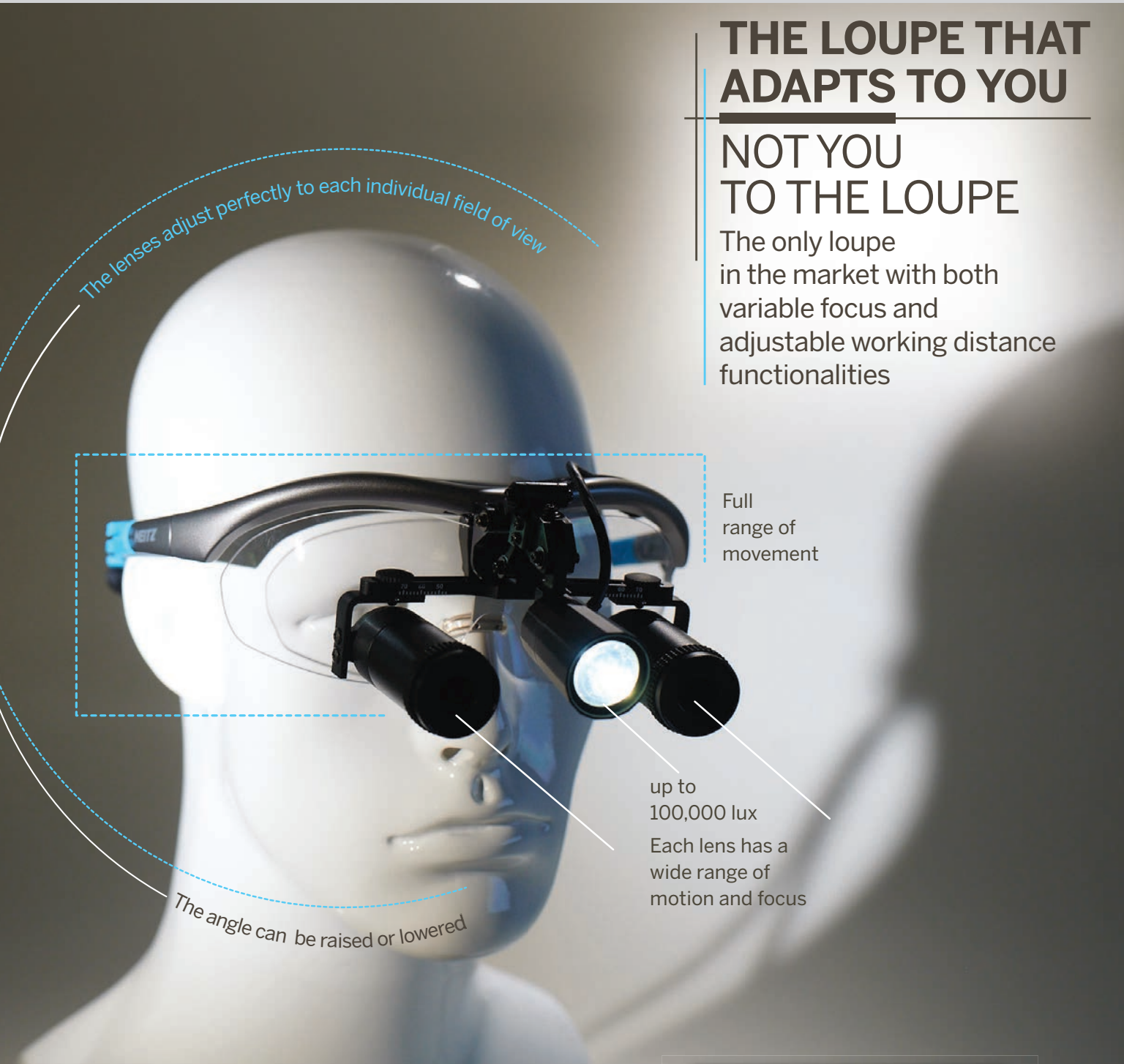

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patient education and IOL selection or, as Dr. Aker describes his role, "medical science liaison between surgeons and patients." Dr. Aker adds: "Dr. Rapp has the scientific knowledge needed to grasp the technical and surgical aspects of what we do, yet he's very adept at communicating to patients in a way that conveys the correct information succinctly without overwhelming them with the clinical details of surgery."

Dr. Rapp also assists on a variety of technical issues at the eye center. For example, during the past year, he played a role in 1,500 femtosecond laser cataract procedures, entering patient data, setting criteria for astigmatism correction values and type, inputting capsulotomy locations, and, when applicable, iris registrations. But perhaps Dr. Rapp's greatest impact has been felt in educating and consulting with patients on premium products and services at the eye center

"What we were doing with patients before surgery in the past was a mistake, jamming everything into one visit," says Dr. Aker. "The patient was basically trying to drink from a fire hydrant. After explaining the premium lens options available for his or her eyes, when you announced that it was going to cost more than $6,000 for both eyes, the patient would get a bad case of sticker shock. He or she would look like a deer in the headlights, ready to run from any thought of what we'd just recommended. What Dr. Rapp does that's different is present a series of outcomes, and we're letting the patient choose the outcome, not the price, first."

Dr. Rapp reaches out to potential surgical candidates about a week before their appointments, explaining to them what their visits will entail. "Under the old approach, patients would come into our practice under the assumption that they might have cataracts," Dr. Rapp says. "I tell them if we find a need for surgery, we're going to go through a very detailed series of measurements and study to really identify their individual anatomy. We're going to determine what's going to be the safest procedural method, plus one, two or three types of lenses that will be agreeable. And the lenses are going to work. 'No matter which of them you choose, you're going to have a great result,' I tell them. 'It's just a matter of how far you want to go with the benefits of the latest technologies.'"

The length of Dr. Rapp's calls ranges from 20 minutes to an hour, during which he asks many detailed questions to focus on patients' visual needs and desires. "'What do you do when you wake up in the morning—do you put your glasses on?'" I ask them. "Do you like your glasses or do you hate your glasses? Do you drive at night? What kind of activities do you like?' Through these conversations, I walk them through every potential outcome. That gives them time to research the options and think about what they might really like. They can converse with their friends, family and spouses to get comfortable with their choices.

THE PRIVATIZATION OF SURGERY?

Is the federal government gradually privatizing cataract surgery? It would seem that way to some surgeons. If you're maintaining a robust surgical practice, investing more in diagnostic technologies, a bigger and better support staff, marketing muscle and facilities needed to deliver premium cataract surgery, you may share this sentiment. If you're sticking to basic cataract surgery, you may also be wondering how you'll get by when shrinking reimbursements from Uncle Sam turn your care and service into a commodity business that you can't continue running on your own.

"What we do for a living is definitely moving toward privatization, to a large extent," says Alan B. Aker, MD, who owns and operates the Aker Kasten Eye Center with his wife, Ann Kasten, MD, in Boca Raton, Florida. "When I got into practice in 1980, reimbursement for cataract surgery was $2,800 per eye. Now Medicare pays $547 per eye. We do commercial cataracts (through HMOs), primarily in hopes that patients will want to upgrade to the femtosecond laser and premium intraocular lenses to benefit from the best care and outcomes that we're able to offer. But some of these patients are only interested in basic surgery, or they're not appropriate for premium lenses."

The typical fee Dr. Aker earns for one of these basic "commercial" cataract procedures ranges from $350 to $400, he says. "When you subtract the other fees that are involved, our fee decreases to $280 for cataract surgery," he points out. "Think about that. That's insane."

As cuts in cataract surgery reimbursements have accelerated during the past 20 years, Dr. Aker notes that many surgeons have worked hard to maximize efficiencies, decrease procedure time, reduce complications, increase volume and improve outcomes. However, these strategies, especially those focused on increased speed and volume, can't be used to gain, or in some cases, maintain ground in today's practice economics—especially as practices invest more in the human and technical resources and consultative time needed to build premium practices that can provide a hedge against the erosion of revenue earned from Medicare.

"With these premium IOLs, the lens manufacturers are trying to eliminate dysphotopsias, which have been the Achilles heel of premium IOLs," Dr. Aker observes. "If we can minimize the halos and glare, patients will want those lenses. Is that bad? Well, we're selling expensive lenses because the patient wants better products. The government says they can buy these better products. And to offer premium lenses, we need to increase the cost of what we do. That's why it's called a premium package."

Dr. Aker acknowledges that continuing cuts in reimbursements may not represent the complete privatization of cataract surgery. "But the survival of practice is involved," he adds. "If the reimbursement goes below $500, I believe a lot of doctors will stop doing routine cataract surgery. They'll opt out and make more money by fitting contact lenses than they will by sweating it out in the OR with a difficult case. The alternative is to embrace new ways of practice. We'll still do the regular cases, recognizing that a lot of patients can't afford to pay for a premium lens. But if surgeons can supplement the regular cases by doing enough of the premium cases, then they can make it. Their practices can be strengthened financially. It's really all about basic practice economics." *—SM*

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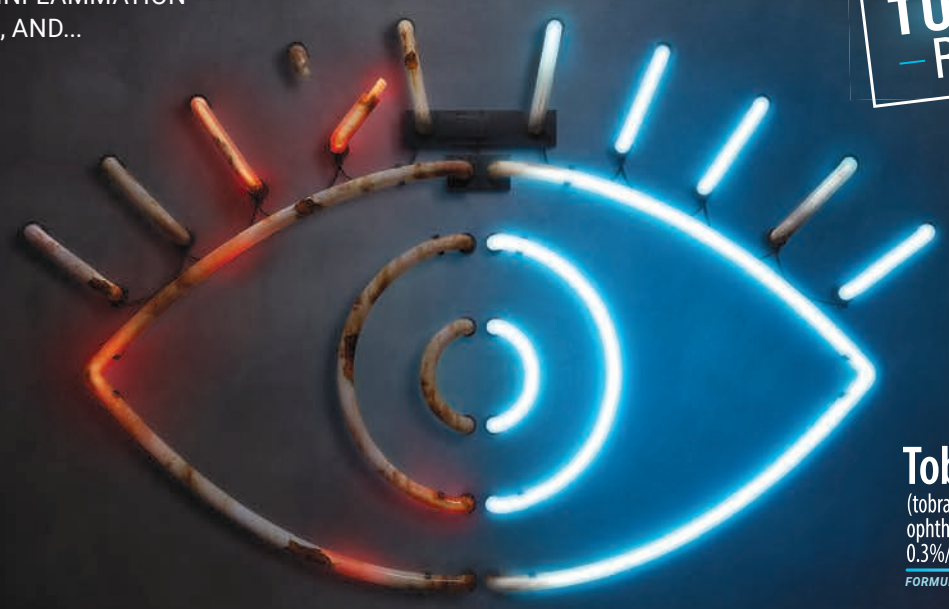

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Indications and Usage

For steroid responsive inflammatory ocular conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe and chronic anterior uveitis, corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies for which a corticosteroid is indicated and where the risk of superficial bacterial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

Important Safety Information

CONTRAINDICATIONS:
Most viral disease of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures. Hypersensitivity to any components of the medication.

WARNINGS & PRECAUTIONS:

- **IOP increase** – Prolonged use may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. IOP should be monitored.
- **Aminoglycoside sensitivity** – Sensitivity to topically applied aminoglycosides may occur.
- **Cataracts** – Posterior subcapsular cataract formation may occur.
- **Delayed healing** – May delay healing and increase the incidence of bleb formation. Perforations of the cornea or sclera have occurred. Slit lamp biomicroscopy, and fluorescein staining should be conducted.
- **Bacterial infections** – May suppress host response and increase secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- **Viral infections** – Use with history of herpes simplex requires great caution. The course and severity of many viral infections of the eye (including herpes simplex) may be exacerbated.
- **Fungal infections** – Fungal infections of the cornea may occur and should be considered in any persistent corneal ulceration.
- **Use with systemic aminoglycosides** – Total serum concentration of tobramycin should be monitored.

ADVERSE REACTIONS:
The most frequent adverse reactions (<4%) to topical ocular tobramycin are hypersensitivity and localized ocular toxicity, including eye pain, eyelid pruritus, eyelid edema, and conjunctival hyperemia.

The reactions due to the steroid component are increased intraocular pressure with possible development of glaucoma, and infrequent optic nerve disorder; subcapsular cataract; and impaired healing.

The development of secondary infection has occurred. Fungal infections of the cornea may occur. Secondary bacterial ocular infection following suppression of host responses also occurs.

Non-ocular adverse events (0.5% to 1%) included headache and increased blood pressure.

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

[a]Randomized, investigator-masked, active-controlled, parallel-group trial conducted at 7 private practice clinical sites in the United States with 122 adult patients who had moderate to severe blepharitis/blepharoconjunctivitis.[1]

[b]Multicenter, double-blind, parallel-group, single-dose study of 987 patients receiving a single dose of TOBRADEX ST or TobraDex ophthalmic suspension.[2]

References: 1. Torkildsen GL, Cockrum P, Meier E, et al. *Curr Med Res Opin.* 2011;27(1):171-178. **2.** Scoper SV, Kabat AG, Owen GR, et al. *Adv Ther.* 2008;25(2):77-88.

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TOBRADEX® ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

Brief Summary

This Brief Summary does not include all the information needed to use TOBRADEX ST safely and effectively. Please see Full Prescribing Information for TOBRADEX ST at MyTobraDexST.com.

INDICATIONS AND USAGE

TOBRADEX ST is a topical antibiotic and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

DOSAGE AND ADMINISTRATION

Recommended Dosing: Instill one drop into the conjunctival sac(s) every four to six hours. During the initial 24 to 48 hours, dosage may be increased to one drop every 2 hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

CONTRAINDICATIONS

Nonbacterial Etiology: TOBRADEX ST is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Hypersensitivity: Hypersensitivity to any component of the medication.

WARNINGS AND PRECAUTIONS

IOP increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. IOP should be monitored.

Aminoglycoside sensitivity: Sensitivity to topically applied aminoglycosides may occur.

Cataracts: May result in posterior subcapsular cataract formation.

Delayed healing: May delay healing and increase the incidence of bleb formation after cataract surgery. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids.

Bacterial infections: May suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Viral infections: Treatment in patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal infections: Fungal infections of the cornea are particularly prone to develop with long-term use. Fungal invasion must be considered in any persistent corneal ulceration.

Use with systemic aminoglycosides: Use with systemic aminoglycoside antibiotics requires monitoring for total serum concentration of tobramycin.

ADVERSE REACTIONS

The most frequent adverse reactions to topical ocular tobramycin (TOBREX®) are hypersensitivity and localized ocular toxicity, including eye pain, eyelids pruritis, eyelid edema, and conjunctival hyperemia. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Non-ocular adverse events occurring at an incidence of 0.5% to 1% included headache and increased blood pressure.

The reactions due to the steroid component are: increased intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve disorder; subcapsular cataract; and impaired healing.

Secondary Infection.
The development of secondary infection has occurred. Fungal infections of the cornea are particularly prone to develop with long-term use. Fungal invasion must be considered in any persistent corneal ulceration. Secondary bacterial ocular infection following suppression of host responses also occurs.

USE IN SPECIFIC POPULATIONS

Pregnancy and Nursing Mothers

There are no adequate and well controlled studies in pregnant women. TOBRADEX® ST ophthalmic suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised when TOBRADEX® ST is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

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

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And we talk about prices, too, well before they come into the eye center."

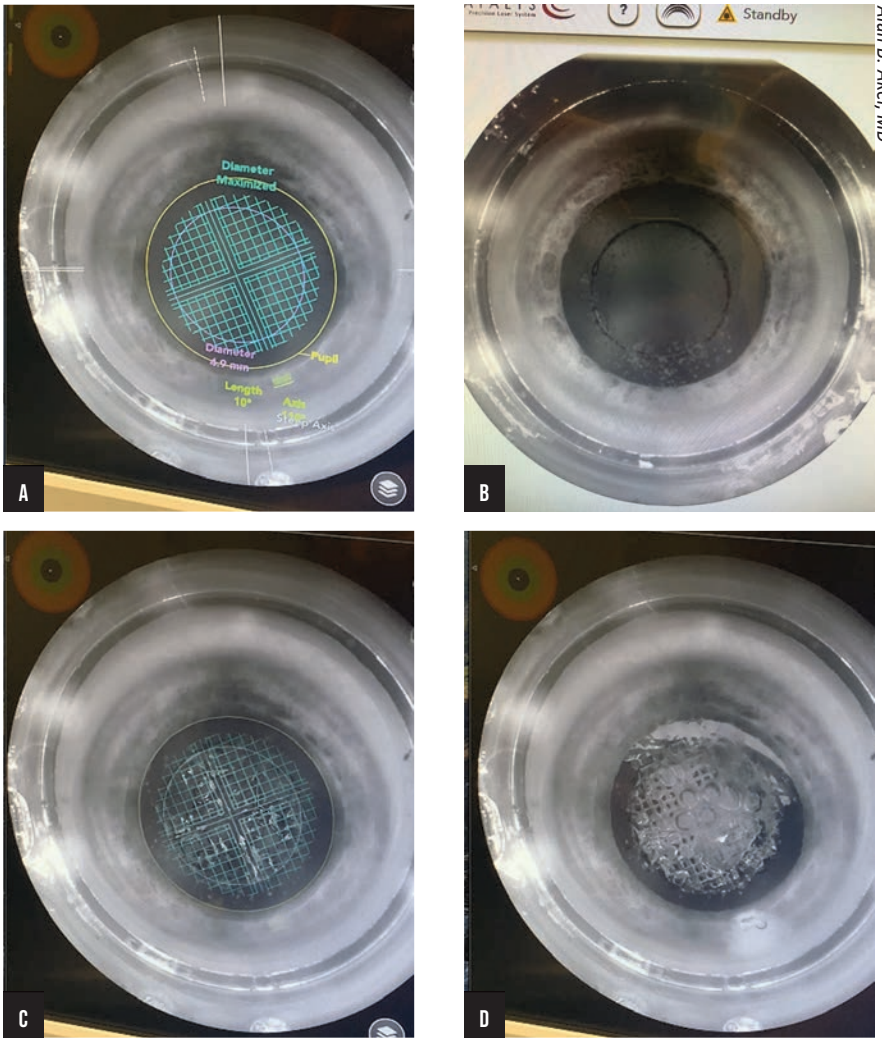
To Femto or Not To Femto?

Many surgeons who launch or expand premium cataract surgery practices employ, at least temporarily, the use of the femtosecond laser or the Zepto (for capsulotomies). In addition to performing some of the steps of the cataract procedure, the femtosecond laser can also create corneal incisions to correct astigmatism.

The balance sheet challenge of using femtosecond laser, including purchase prices of up to $500,000 and pricey usage fees and maintenance contracts, often determines if surgeons will use the technology as a permanent service. Other factors can also play a role.

"I'd say the femtosecond laser is a great technology," says Dr. Patterson, whose practice leased a femtosecond laser for cataract surgery from 2015 to 2017. "For our system, however, in which we used the femto in one room and performed the surgery in our single OR, it slowed us down and it didn't change our refractive outcomes. Femto gave us great outcomes, but we had manual outcomes that were just as good. Therefore we decided it wasn't in the best interests of our company to continue with the technology."

He adds that the financial burden of femto on patients was also a consideration. "We were already charging patients for a premium lens outcome, not a process," he says. "In our demographic, our patients are much more interested in premium technology when the price is reduced. When we were using femto, we had to charge an extra $1,000 to $1,500. Now that we've removed that charge, more patients have adopted the lens technology. We practice in a rural setting. As I mentioned, we don't practice where there's a lot of money. So these were the main considerations involved."



Alan B. Aker, MD

Figure 4 A-D. When the femtosecond laser is used in cataract surgery, the first step (A) is the establishment of safety limits by the iris perimeter, maximizing the diameter. A perfectly centered capsulorhexis follows, completed in two seconds (B). The waffle pattern on the lens (C) shows one of several laser pulses as it softens the cataract. Fragmentation of the lens generates gas bubbles that help dissect the nucleus of the cataract (D).

Dr. Greenwood was similarly impressed by the femtosecond laser when he used it at his practice for a limited period. "I learned a lot from it," he says. "We're all good cataract surgeons, of course, but we can't do what a laser can do. It's more precise."

Dr. Greenwood used the lessons he learned from femto to create a capsulotomy with sufficient overlap to ensure that it contracted around the optic, leading to better centration and less chance of IOL tilt. "These techniques ensure the superior visual outcomes surgeons are seeking from premium IOLs," he says. He notes that femto also taught him the visual significance of a half-diopter of astigmatism and the benefits of correcting astigmatism below 1 D, the lowest correction level treated by toric IOLs. "That's when using the femtosecond laser to create some arcuate incisions was really helpful," he adds. "With some of the femtosecond platforms, you're able to use the femto technology for toric IOL markings. I think the femtosecond laser is a very nice tool, and it's up to individual surgeons

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INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

IMPORTANT SAFETY INFORMATION

- PROLENSA® contains sodium sulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
- All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Use with caution in patients who have previously exhibited sensitivities to these drugs.
- There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Use with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

IMPORTANT SAFETY INFORMATION (CONT.)

- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.
- PROLENSA® should not be instilled while wearing contact lenses. The preservative in PROLENSA®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA®.
- The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

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

References: 1. PROLENSA Prescribing Information. Bausch & Lomb Incorporated. **2.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of (14)C-labeled bromfenac following topical instillation into the eyes of New Zealand white rabbits. *J Ocul Pharmacol Ther.* 2008;24(4):392-398. **3.** Data on file, Bausch & Lomb Incorporated.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Prolensa safely and effectively. See full prescribing information for PROLENSA®.

PROLENSA® (bromfenac ophthalmic solution) 0.07%

Rx only
Initial Rx Approval: 1997

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is indicated for the treatment of postoperative inflammation and reduction of pain in patients who have undergone cataract surgery.

DOSAGE AND ADMINISTRATION

Recommended Dosing

One drop of PROLENSA ophthalmic solution should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

Use with Other Topical Ophthalmic Medications

PROLENSA ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time

With some NSAIDs, including bromfenac, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that PROLENSA ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

PROLENSA should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

ADVERSE REACTIONS

Clinical Trial Experience

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

The most commonly reported adverse reactions following use of PROLENSA ophthalmic solution following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia and vision blurred. These reactions were reported in 3 to 8% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

Treatment of rats at oral doses up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality, and reduced postnatal growth at 0.9 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of PROLENSA ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when PROLENSA is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

Geriatric Use

There is no evidence that the efficacy or safety profiles for PROLENSA differ in patients 70 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively, revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests. Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents. Advise patients that a single bottle of PROLENSA be used to treat only one eye.

Concomitant Use of Contact Lenses

Advise patients to remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart.

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to decide whether it's beneficial for them and their patients or not."

Why hasn't he continued with femto? "For a variety of reasons," he says. "For us, as the IOL and lens technology got better, the benefits that the femtosecond laser were providing us were not as great as some of the hurdles, whether it be cost or inefficiency or technique and things like that."

He notes that the availability of the Light Adjustable Lens (RxSight), now able to correct very small amounts of astigmatism, has provided another reason the femtosecond technology isn't always necessary. "For patients who have a very small amount of astigmatism, maybe the toric IOL isn't appropriate for them, but the Light Adjustable Lens can take care of that need," he says.

From Doubter to Doer

Dr. Aker says he originally opposed the use of the femtosecond laser because of the challenging financial model it presented. Now he offers it to every patient because he says it provides the best outcomes for the cornea and the capsulorhexis. He recalls realizing one day that he and his partner/wife, Dr. Kasten, were not using the technology correctly. "If this technology provides better, safer surgery, then we should be using it on all patients, not just premium ones," he reasoned.

He and Dr. Kasten have used an alternative pricing strategy to make femto work in their practice. "We have practices in our area charging $4,500 per premium lens, and we're at $3,300," he notes. "Or practices will charge what we charge and add $1,500 for the femtosecond laser. Instead, we now add $300 to our premium lenses across the board and we add $1,500 to the cost of regular cataract surgery for the femtosecond laser. For premium patients, they just see the cost of the lens. And included in that is a femto procedure. If the patient is paying for a premium result, there's no way I'm going to do a sub-premium cataract procedure for him or her. We use femto to protect the cornea (via the use of less phaco energy), correct less than a diopter of astigmatism and achieve a perfect final lens position."

Dr. Aker says he explains to patients that he can use his experienced surgeon's hands to perform a near perfect capsulorhexis, and that he can protect the cornea with viscoelastic solutions. '"But I can't protect your cornea as well as the femtosecond laser does when it softens a cataract,"' he says.

How to Go Premium

Whether it's with a femtosecond laser or not, surgeons who're expanding their premium cataract practices offer some basic advice for you to follow to find out how to do the same in your practice:

- Talk to peers who are doing it;
- consult with IOL and diagnostic technology reps, who are well-versed on how other surgeons are doing it;
- make it your mission to learn what you can at state, regional and national ophthalmology meetings, either from lectures or from colleagues with whom you can network; and
- avoid bad word-of-mouth perceptions of your practice, which can invalidate the sharpest marketing efforts.

"Some doctors need to purchase the diagnostic technology that makes this type of practice possible and some already have the technology, but they don't understand how to use it yet," says Dr. Patterson. "It's like an iPhone. You sometimes don't really have a clue what technologies are on it until somebody helps you with it. It's amazing what it can do. You have the technology; you just don't know how to use it. That same principle applies to lens and device technology."

Dr. Greenwood recommends that you avoid negative outcomes at all costs. "If you ask patients to pay for a premium intraocular lens, and there's residual refractive error or they experience less than ideal outcomes, they're not going to be happy," he says. "They're going to tell their friends and other potential patients that they didn't feel they got any benefit from the premium lenses they paid extra for." He recommends offering patients a premium "package" price that includes all enhancements such as LASIK, PRK, IOL rotations or a full IOL replacement at no extra charge to ensure patients are completely satisfied.

"Make sure every one of your patients gets into the endzone," he continues. "Keep your offerings simple. Everyone in your practice–particularly a few key people–needs to be very comfortable discussing financials with the patients. And it's really helpful if the doctor is one of them, because the doctor is the one introducing the surgery. If the doctor can at least begin to discuss pricing with the patient, that typically is very helpful. You want to provide follow-up for these cases that's not different from what was outlined in the original plan, whether it's a second procedure or the possibility of another surgeon needing to do the follow-up because of his or her expertise or role in the practice. Patients are very happy, trusting and encouraged by these approaches. It takes a little time and effort on the front end. But having a plan in place and discussing it with the patient is very helpful."

Intraprofessional Trust and Support

"I welcome any surgeon who's interested in getting involved in premium products and services to come visit us," says Dr. Aker, who will join Dr. Rapp to present their approach to building a premium cataract surgery practice at an upcoming meeting of the Palm Beach County Ophthalmology Society. "Find out how it works and see how we do it. When we share information like this, it benefits all of our practices." ◀

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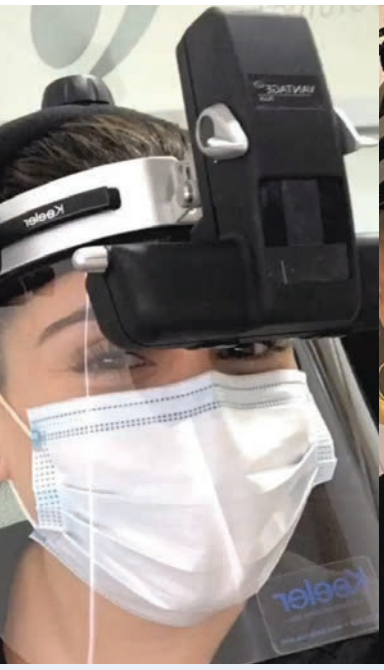


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Dr. Reza Moradi

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MINIMIZING COMPLICATIONS IN TRABECULECTOMY

Experts offer pearls for ensuring the best possible outcomes, and debate whether trabs still make sense.

CHRISTOPHER KENT
SENIOR EDITOR

Although trabeculectomy is a powerful tool for a glaucoma surgeon, it comes with risks, some of which—although rare—are quite serious. Today, as the glaucoma surgery landscape evolves, the risk/benefit ratio associated with trabeculectomy keeps changing. If the risks associated with this surgery get smaller, but a failure is still potentially catastrophic, how do you respond? As more alternatives to trabeculectomy appear and slowly evolve, how does that change the equation?

Many surgeons still believe that trabeculectomy is irreplaceable, but to justify that position, it's important to do everything possible to reduce the risks associated with this surgery. Unfortunately, a successful trabeculectomy isn't just a question of surgeon skill. Marlene R. Moster, MD, a professor of ophthalmology at the Sidney Kimmel Medical College at Thomas Jefferson University and an attending surgeon at Wills Eye Hospital Glaucoma Service in Philadelphia, notes that being an excellent surgeon experienced at performing trabeculectomies isn't enough to ensure a great outcome. "Even if all goes smoothly in the OR," she says, "unpredictable complications may occur postoperatively."

Here, surgeons with extensive experience performing trabeculectomies offer advice on ways to reduce the different risks associated with the surgery, and share their thoughts about trabeculectomy's place in the surgical armamentarium.

Preoperative Issues

To help minimize the chance of unwanted complications, several issues should be addressed before the surgery:

• ***Manage any ocular surface inflammation.*** "Preop, we need to treat any inflammation we find, because inflammation on the ocular surface can affect the outcome," says Reza Razeghinejad, MD, an associate professor of ophthalmology at the Sidney Kimmel Medical College of Thomas Jefferson University, and director of the glaucoma fellowship program at Wills Eye Hospital in Philadelphia. "For example, a patient may have follicular conjunctivitis or allergic contact dermatitis because of topical medication use. (*See figure, facing page.*) We need to stop the topical medication in these patients at least one week before surgery. I also start oral medication, because when you have a lot of inflammation you may have a lot of bleeding during the surgery, which can cause subconjunctival hemorrhages. That will eventually cause the procedure to fail."

"Inflamed red eyes may be prone to scarring and early failure, and one of the reasons to do a trabeculectomy is to eliminate the need for topical medications, which in some cases can negatively affect both the cornea and vision," says Dr. Moster. "When the patient needs to come off medication before surgery, I substitute oral acetazolamide and non-preserved artificial tears for a week, giving the eye a drop holiday. In addition to the preop topical steroids, I've tried using over-the-counter Lumify to whiten up the eye prior to surgery.

"It's not always easy to take the

This article has no commercial sponsorship.

Dr. Iwach is a consultant to Ivantis and New World Medical and is on the speaker's bureau for Bausch + Lomb and New World Medical. **Dr. Singh** is a consultant for Alcon, Allergan, Santen, Sight Sciences, Glaukos and Ivantis. **Drs. Moster** and **Razeghinejad** report no relevant financial disclosures.

patient off of medications," she adds. "However, it's my clinical impression that when the pressure is very high and the eye is very red, the medications aren't working anyway."

• ***Make sure blood pressure is controlled.*** "If the patient has high blood pressure, we need to make sure the blood pressure is controlled," says Dr. Razeghinejad. "Uncontrolled blood pressure is a risk factor for suprachoroidal hemorrhage or effusion."

• ***Make sure intraocular pressure isn't too high.*** "We also need to lower a high IOP before surgery—at the very least in the preop area before bringing the patient back to the operating room," Dr. Razeghinejad notes. "We can do this using an intravenous medication such as mannitol or acetazolamide. If we start the surgery with a very high IOP, as soon as we decompress the eye there's a chance we may get suprachoroidal hemorrhage. If we can't offer intravenous medications, we can create the side port first and lower the eye pressure gradually by accessing the side port before starting the surgery."

Dr. Moster agrees. "If it's not possible to lower the pressure before surgery, do a paracentesis in the OR at the start of the surgery," she suggests. "Bring the IOP down to about 20 mmHg—not too low or too high. That will give the eye time to equilibrate."

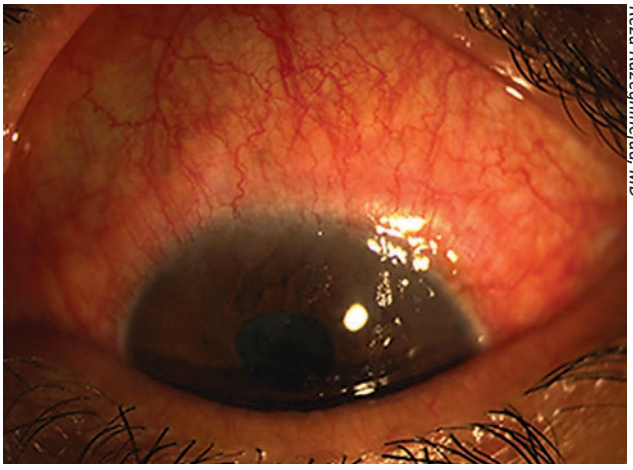
• ***Address the issue of blood-thinning medications.*** "Stopping blood thinners before surgery isn't mandatory, but some surgeons do prefer to stop them," notes Dr. Razeghinejad. "In that case, we need to coordinate with the primary care physician or cardiologist to make sure they're OK with stopping the medication. In the meantime, when we stop it, we can put the patient on heparin, which has a short half-life. We can use that for a few days before taking the patient to the OR.

"The concern, of course, is getting bleeding in the subconjunctival space," he continues. "This can eventually cause fibrosis and scar formation and failure of the procedure. *(See image, p. 52)* Or, we may get bleeding in the anterior chamber when we're doing a peripheral iridectomy.

"These days, most glaucoma surgeons aren't stopping the blood-thinning medications," he concludes. "If you stop the medication and the patient develops a CVA or emboli, you'll create another problem."

Dr. Moster agrees. "I don't typically stop blood thinners before the surgery due to the added risk of thromboembolic events," she says. "We use topical, subconjunctival and intracameral lidocaine for anesthesia during a trabeculectomy, and avoid retrobulbar or peribulbar blocks entirely. This decreases the risk of an orbital bleed."

• ***Set realistic patient expectations.*** "Before the surgery I usually have a long discussion with the patient about possible complications and postoperative IOP fluctuations," says Dr. Razeghinejad. "When discussing possible complications, I talk about three major things: bleeding; infection; and effusion. In terms of the outcome, I explain that the pressure could be too low or too high after the surgery, and the patient may need to tolerate some adjustments during the first few weeks after surgery. I also explain that if this procedure fails, the patient may need to go back to the OR to do a revision or a shunt procedure. I prepare them for multiple possibilities, because we don't know the nature of the healing process for each patient. It's totally individualized."



Reza Razeghinejad, MD

Inflammation on the ocular surface preop must be addressed; it can affect the outcome. Above: follicular allergic conjunctivitis secondary to the use of topical glaucoma medications.

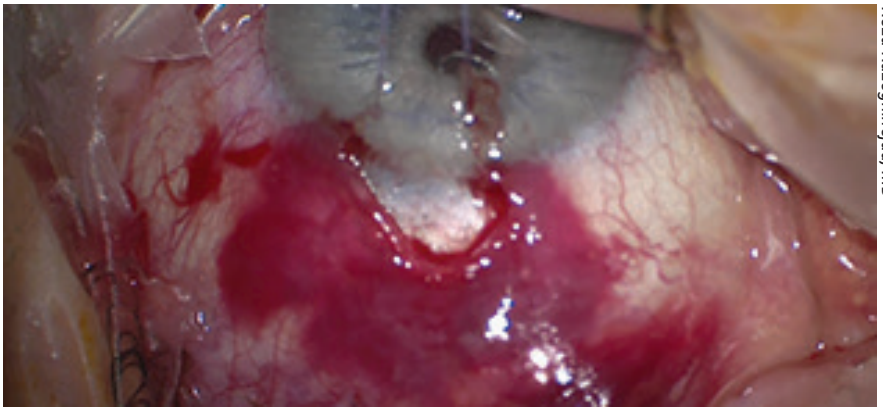
Intraoperative Concerns

Dr. Moster notes that most complications occur postoperatively, not intraoperatively. Nevertheless, there are issues that can arise during the surgery. "Intraoperatively, the four things to look out for are suprachoroidal hemorrhage, malignant glaucoma, excessive unanticipated bleeding in the anterior segment, and a flat chamber caused by excessive aqueous flow," she explains. "Fortunately, these are pretty rare."

Dr. Moster offers this advice for managing these issues, should they arise:

• ***Malignant glaucoma.*** "Sometimes this occurs during a trabeculectomy," she notes. "The eye becomes incredibly hard due to aqueous being trapped behind the lens. That's a very uncomfortable situation for both the patient and the surgeon.

"Ultimately, to manage malignant glaucoma, medications are tried first," says Dr. Moster. "If those are not successful, either a YAG laser rupture of the vitreous face or a surgical vitrectomy is needed to create a unicameral eye; an iridectomy is always required to eliminate the pos-



Reza Razeghinejad, MD

A subconjuctival hemorrhage occuring during trabeculectomy. This type of unexpected complication can eventually lead to bleb failure.

sibility of pupillary block. Once the diagnosis is made, the pupil can be dilated and mannitol administered intravenously, which may break the attack. If that isn't successful, a vitrectomy will need to be performed to disrupt the anterior vitreous face. Often, the aqueous has readjusted by the next day, the chamber has increased in depth and the intraocular pressure has stabilized. Pupillary dilation is maintained throughout the postoperative course.

"More often than not, in a pseudophake, you can disrupt the vitreous face directly through the iridectomy," she notes. "Noemi Lois, MD, showed that in a pseudophakic eye, a vitrector can be used to go through the iris, the zonules and the anterior vitreous face to make a unicameral eye, breaking the attack, in almost every case. A phakic eye is a lot more worrisome. If the chamber is shallow and the pressure is high, then the patient will need a retina consult for a full vitrectomy in order to reverse the aqueous misdirection."

• ***Bleeding.*** "Another common problem that can occur is increased bleeding due to blood thinners," notes Dr. Moster. "As noted, I don't typically stop blood thinners before the surgery due to the added risk of thromboembolic events. Usually, we can control surface bleeding without incident. However, on occasion there can be bleeding during an iridectomy, and it's impossible to predict."

• ***A flat chamber.*** "During the trabeculectomy, try to prevent the chamber from flattening," advises Dr. Moster. "It's best to avoid hypotony so that choroidals don't develop during the procedure. That's especially true for high myopes, where a tube, ExPress Shunt or GATT procedure might be a better choice. I prefer a GATT for some myopes, to avoid the need for mitomycin-C and the risk of hypotony maculopathy.

"In rare cases the chamber may flatten because there's too much outflow under the scleral flap, and more sutures are needed to control the situation," she adds. "In general, it's never a good idea to leave the chamber flat. We always try to reinflate the eye quickly using balanced salt solution or viscoelastic to deepen the eye, and then close the scleral flap up tight to re-establish the anatomy. The releasable or laserable sutures can later be removed for postoperative pressure control."[1]

• ***Suprachoroidal hemorrhage.*** "This is another feared complication of trabeculectomy," Dr. Moster notes. "While doing the trabeculectomy, one of the posterior blood vessels within the choroid can rupture. This is akin to an air-bag explosion, and the chamber becomes shallow. When the IOP is elevated, you must close that eye very quickly to avoid an expulsive hemorrhage."

Dr. Razeghinejad notes several surgical issues that can reduce or increase the likelihood of complications during the operation:

• ***Placing the traction suture.*** "The location of the traction suture can be an issue," he says. "Previously, everybody was putting the traction suture under the superior rectus, but these days most surgeons prefer to use a clear-cornea traction suture. This seems to be safer because there are a lot of blood vessels around the superior rectus muscle; when you pass the needle through, you can get a subconjunctival heme, leading to more fibrosis and surgery failure."

• ***Making the peritomy.*** "Before creating the peritomy, we inject mitomycin-C, in all patients," Dr. Razeghinejad says. "We usually inject 0.1 ml of a 0.4-mg/ml concentration, mixed with 2% lidocaine. We inject this under the conjunctiva about 5 mm posterior to the limbus before opening the conjunctiva. Patients who are young and highly myopic are prone to hypotony after trabeculectomy, so for those patients we may use a concentration of 0.2 mg/ml instead of 0.4.

"To open the conjunctiva you have two different possible approaches: a fornix-based peritomy or a limbus-based peritomy," he continues. "Overall, fornix-based peritomies are preferred because we have better exposure, and the likelihood of the bleb extending to the posterior is higher."

• ***Creating the scleral flap.*** "The surgeon can create many different flap shapes," notes Dr. Razeghinejad. "Overall, there's no major difference between them. There's only one major concern when creating the flap—to avoid cutting beyond the area in which there's original conjunctival attachment to the limbus. (*See picture, p. 55*) If we do that, we may get postop leakage and a

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shallow anterior chamber. Also, in patients who have low scleral rigidity—for example, those with congenital glaucoma or high myopia—we should avoid creating a large scleral flap, because it will cause a significant amount of astigmatism."

• ***Making the ostomy.*** "When making the ostomy we should avoid going too far posteriorly because it can cause bleeding," explains Dr. Razeghinejad. "It can also cause a cyclodialysis cleft, or even vitreous loss."

• ***Creating a peripheral iridotomy.*** "Whether or not a PI is done depends on the surgeon and the patient's condition," Dr. Razeghinejad notes. "For example, if a patient has had previous cataract surgery, doing a PI isn't mandatory, but if the patient is phakic, he definitely needs the PI.

"When making a PI it may be better to avoid injecting lidocaine intracamerally," he continues. "Injecting lidocaine can cause pupillary dilation and make the PI harder to do. Also, in patients who have a short eye or plateau iris syndrome, we need to be aware that the ciliary processes are a bit anterior. We should avoid cutting them in the process of making the PI."

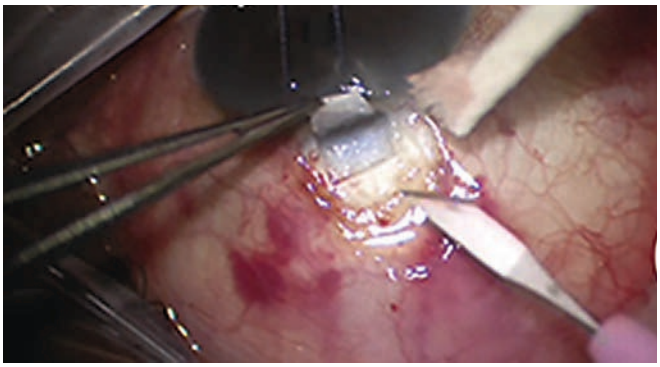
• ***Closing the flap.*** "We may use interrupted permanent sutures or releasable sutures to close the scleral flap," notes Dr. Razeghinejad. "If we're just using non-releasable sutures for closing the flap, it's better to have a long-arm suture, because it's easier to bury it. Also, if we're doing suture lysis after the surgery, finding the suture is easier."

• ***Closing the conjunctiva.*** "Some surgeons use 10-0 nylon to close the conjunctiva; some use 8-0 vicryl sutures," says Dr. Razeghinejad. "If you use 8-0 vicryl, it's better to use the vascular needle instead of the cutting or spatulated needles because the latter can cause conjunctival buttonholing. However, if you're using 10-0 nylon sutures, you can use any needle. The hole created in the conjunctiva is very small, and you're not concerned about tearing the conjunctiva and having leakage."

Dr. Moster adds that it's helpful to take steps to minimize postoperative scarring. "To help avoid this, I use a small amount of intracameral steroid, such as non-preserved triamcinolone, and when possible, a steroid pellet like Dextenza placed in the inferior punctum," she explains. "This helps to address the issue of poor compliance with topical steroids postoperatively."

Postop Complications

"There are a number of issues we need to address during the postop period, including astigmatism from sutures, cataract formation and the remote possibility of endophthalmitis," says Dr. Moster. "The releasable suture usually comes out between one and three weeks; the vicryl running suture closing the fornix-based flap will dissolve by itself. Patients are usually on antibiotics for only one week. If the chamber is shallow, I dilate the


Reza Razeghinejad, MD

The radial incisions for the scleral flap shouldn't go beyond the line of original conjunctival attachment to the limbus surgeons say.

eye; if not, I don't.

"The goal," she adds, "is to stop all glaucoma medications postop."

One major issue to manage is the use of postoperative steroids. Dr. Razeghinejad advises being generous about their use. "After the surgery we see a lot of conjunctival inflammation," he explains. "Using a good amount of steroid is really important, because if we don't, the inflammation may promote the healing process and eventually lead to fibrosis and failure of the procedure."

"I start the steroids four times a day for two weeks, tapering down by one drop each week," notes Dr. Moster. "That makes a total of eight weeks of steroids."

"The amount of steroids we use depends on the amount of inflammation and congestion we see in the bleb area," says Dr. Razeghinejad. "We may need to put some patients on a steroid every two hours for the first few days after the surgery. Depending on the congestion, we may need to keep the patient on the steroid for three or even four months—although in some cases, we may be able to stop the steroid after a month or two. If the patient doesn't respond to the steroid drops and we see a lot of congestion, we can inject mitomycin-C or 5-FU under the conjunctiva around the bleb area to delay the healing process and keep the bleb functioning."

Other issues that may arise in some patients include:

• ***Scarring that interferes with outflow through the bleb.*** "This can happen either early or late within the postop period," notes Dr. Moster. "It can be managed by needling the bleb with the addition of MM-C or 5-FU."

"Bleb needling can be done in the office," notes Dr. Razeghinejad. "Sometimes it works; sometimes not. If it doesn't work, we need to go under the flap with the needle and lift the edge of the flap. As soon as we see some flow under the conjunctiva, we can take the needle out. It may be helpful to inject some 5-FU or MM-C under the conjunctiva.

"Eventually, if all of these fail," he adds, "we need to consider doing a bleb revision, or a tube shunt surgery."

Dr. Moster says the ability to use needling to potentially resolve this problem is one reason she prefers trabs as first-line rather than tubes. "If the trab fails, needling will bring it back to life in about 64 percent of cases," she says.[2] "Unfortunately, tubes are not amenable to this."

• ***A plugged ostomy.*** "If the pressure is up after trabeculectomy and we don't have any bleb, first we need to do a gonioscopy," says Dr. Razeghinejad. "Sometimes iris tissue plugs the ostomy you've created. In this situation we can use pilocarpine eye drops a couple of times in the office to take the iris out of the ostomy and release the iris tissue. If that doesn't work, we may do a YAG laser using a goniolens, applying the laser at the interface of the iris tissue and the border of the ostomy. If the IOP remains elevated after the iris is released, we can do suture lysis—cut one of the sutures over the flap, or remove one of the releasable sutures to enhance flow under the conjunctiva. If all of these fail to get the bleb back to normal function, we need to consider doing bleb needling."

• ***A bleb leak from the incisional site.*** "If this occurs, you can try a bandage contact lens, use cautery to close the leak, or take the patient back to the OR and put in an extra stitch," says Dr. Moster. "We always check the wound with a fluorescein strip prior to leaving the OR to make sure the wound is watertight."

• ***Hypotony.*** "Of course, hypotony caused by over-filtration is always a potential issue," says Dr. Moster. "When dealing with postop hypotony, dilate the pupil; consider using viscoelastic to deepen the chamber, or consider putting trans-conjunctival sutures through the bleb to increase the resistance within the bleb.[3]

"A good way to decrease postop complications in general is to use either laserable or releasable sutures to help keep the IOP where you want it," she adds. "I currently use releasable sutures and remove them as needed at the slit lamp. They help control the postop flow during the first three weeks. If the pressure is starting at a higher level, I tie the releasable suture down tight; I don't want the pressure to be very low on the first day."

• ***Tenon's cyst formation.*** "This is something you may occasionally encounter," says Dr. Moster. "It can be addressed by waiting until the cyst softens."

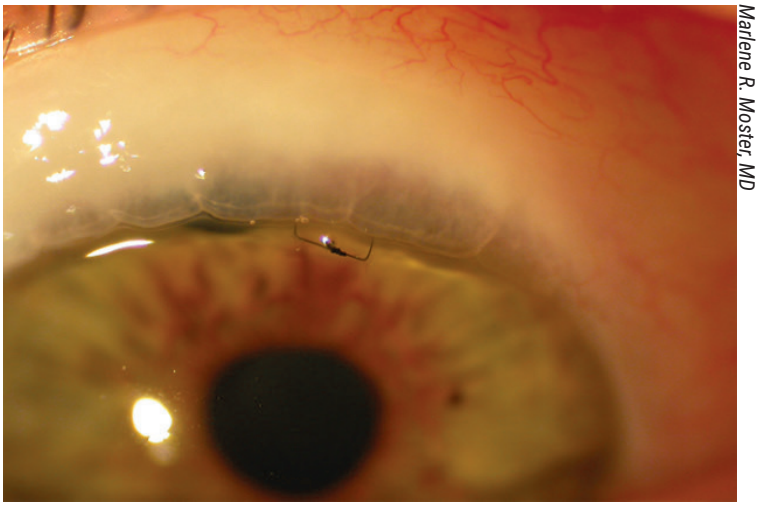
• ***Blebs migrating onto the corneal surface.*** "This occasionally happens," notes Dr. Moster. "Currently, however, we're primarily doing fornix-based flaps, so that both cysts and migrating blebs are becoming a rare phenomenon."

Patient Management Postop

Aside from managing any postop complications that occur, it's important to continue to keep the patient's expectations realistic. "I explain to each patient that early on their vi-

sion will be blurry due to the sutures and fluctuating intraocular pressure," says Dr. Moster. "There are generally one or two sutures that need to be removed by three weeks, but everything else dissolves. Beyond that, I usually tell them it will take about eight weeks to be off all drops and be over and done."

Dr. Razeghinejad says he prepares the patient for the possibility of a problem. "After the surgery, the two major things we're concerned about are suprachoroidal hemorrhage and endophthalmitis," he notes. "Once the surgery is done I usually tell the patient: 'If you have any more pain or redness than what you have now, or any worsening of your vision, you need to call us.' Those symptoms could mean a number of things, so we'll need to examine the patient."



Marlene R. Moster, MD

A releasable suture (above) usually comes out between one and three weeks postop.

Dr. Razeghinejad says he generally sees the patient on day one, and if everything continues to be fine, the next visit is a week later. "Then we'll see the patient every two to three weeks for the first two months after the surgery," he says. "If everything is still OK, we'll see the patient again a month after that. This covers the whole three postoperative months. However, we feel lucky when we have a patient like that; we see most patients more frequently. Sometimes the pressure is high or low postop; we may find a shallow anterior chamber or leakage; or we may find choroidal effusion. It's unusual to have a patient who doesn't need any laser suture lysis or an MM-C or 5-FU injection or other interventions in-office. Most patients need something."

Dr. Moster says she sees patients the day after surgery and at week one. "After that, I see the patient sometime within the following two weeks, to make sure the pressure is at the goal and the releasable suture is out," she explains. "I check them again in one month; then I individualize the timing. Generally, once the wound is stable and the pressure's on target, I send the patient back to the referring doctor.

"Everything has to be individualized to the patient's circumstances," she adds. "The reality is, every patient has a different history, different comorbidities and different ocular issues."

Are Trabs On the Way Out?

It's no secret that use of trabeculectomy has been declining in recent years, with a concurrent increase in the number of tubes being performed. This downward trend in the use of trabeculectomy has led to considerable debate regarding whether trabeculectomy is still a viable choice for patients, and whether the decline in its use may have unintended side effects.

"Fewer and fewer ophthalmologists know how to do a successful trabeculectomy," says Dr. Moster. "It's becoming a lost art. There's a trend toward doing more tubes, but nothing works as well as a good trabeculectomy. I've seen trabeculectomies work well beyond 15 years, with the patients needing zero medications. This has been the case in both Caucasians and African-American patients. So, if someone needs a low IOP, I prefer a trabeculectomy. I'll do everything I can to avoid complications—which is the issue surgeons worry about."

"I think there's still room for trabeculectomy," says Dr. Razeghinejad. "We use it in many situations where other procedures aren't working. For example, it's a good solution for a young patient with pigmentary glaucoma who's concerned about having diplopia following tube shunt surgery. The XEN isn't an ideal choice because these patients have pigment in the anterior chamber that can clog the stent. So trabeculectomy is our only option. If the patient is young and phakic, a GATT or goniotomy procedure may not work, so trabeculectomy seems to be the best option.

"Also, a MIGS procedure may not work for many phakic patients with high pressure that need surgery," he continues. "Most MIGS procedures are based on bypassing the trabecular meshwork, and if you have any problem downstream, the pressure will stay high after the MIGS procedure. Furthermore, most MIGS procedures have to be combined with cataract surgery, and many glaucoma patients don't need cataract surgery."

"Our glaucoma patient population includes an ever-increasing shift towards older age, with proportionately more patients in their 80s, 90s and beyond," notes Kuldev Singh, MD, MPH, a professor of ophthalmology and chief of the Glaucoma Division at the Stanford University School of Medicine in California. "As patients live longer, we'll see more of them

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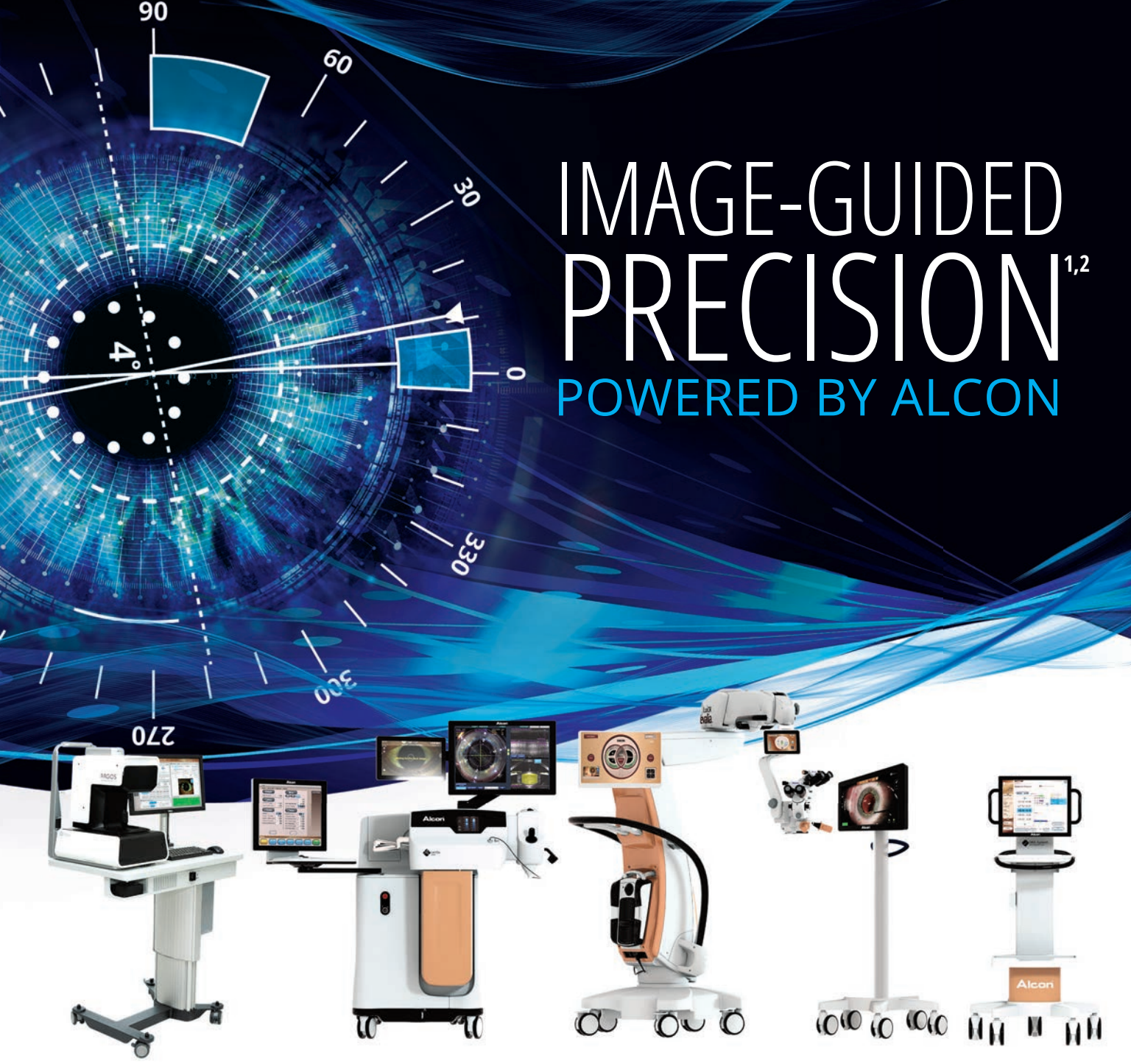

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who will have advanced disease and a need for very low IOPs during their lifetimes, sometimes only attainable with skillfully performed trabeculectomy. Despite this, current circumstances—including the training required to learn trabeculectomy, the substantial postoperative care and insufficient reimbursement associated with this procedure, and the presence of easier, but not as effective options—are moving many surgeons away from performing trabeculectomy in patients who need this procedure.

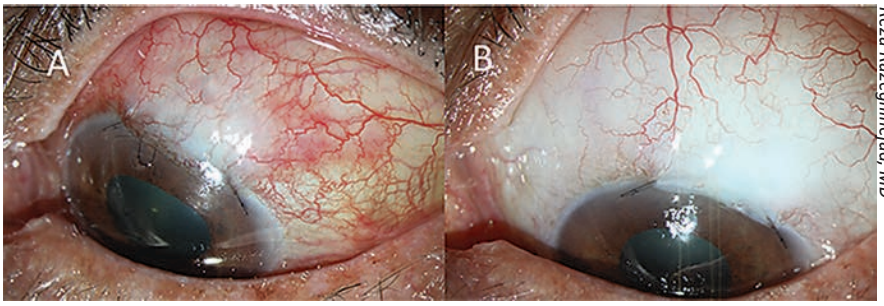
"This trend could lead to a downward spiral of surgeon skill," he points out. "Surgeons experienced with performing trabeculectomy may dwindle in number, leading to more problematic surgical outcomes in the hands of less-experienced surgeons, and, ultimately, fewer surgeons wanting to perform the procedure. Trabeculectomy is in danger of becoming a lost art, which I believe will create a public health problem.

"Despite this trend, a number of studies have confirmed the unique power of a trabeculectomy," he adds. "Studies have shown that trabeculectomy can significantly reduce the likelihood of disease progression,[4,5] improve visual function[6] and produce lower IOPs than other options, when needed.[7] So trabeculectomy is a procedure that very much needs to remain a part of our armamentarium.

"Not every fellowship-trained glaucoma specialist will continue to perform trabeculectomy, and, of course, nobody can force them to do so," he concludes. "But trabeculectomy, when performed skillfully and followed by appropriate postoperative care, is sometimes the best approach to prevent blindness in those with advanced and/or high-risk glaucomatous disease."

Are Tube Shunts the Answer?

Andrew Iwach, MD, the executive director of the Glaucoma Center of San Francisco and an associate clinical professor of ophthalmology at the University of California, says that until a few years ago, he did plenty of filtering surgeries. "The problem with bleb-based surgeries, regardless of your technique, is that they're a setup for potential long-term trouble," he notes. "Blebitis can lead to endophthalmitis, which, although uncommon, can result in a patient who has good vision at the outset losing significant vision or even an eye—a catastrophic outcome.



Reza Razeghinejad, MD

A) A congested bleb, before increasing the steroid dose. B) The same eye four weeks after high-dose topical steroid therapy and removal of the releasable suture.

"About seven years ago I carefully reviewed what we were doing," he says. "At that time, we were modifying our surgical approaches with tube shunts, such as the designs we were using and our technique as to tube and plate placement, to lower risk, and the risk profile for tube shunt surgery started going down. For example, we were doing some research combining tube surgery with subsequent judicious use of laser cyclophotocoagulation. We found that just a little bit of laser as an adjunct could produce excellent results. Only about 25 percent of our tube shunt patients needed the subsequent laser treatment, but the combination showed excellent stability and a low complication rate. (We presented our data on this at the 2019 meeting of the American Academy of Ophthalmology.) With this protocol, the postop follow-up is much simpler and typically safer. This improvement in our tube shunt protocol caused me to begin rethinking the role of trabeculectomy.

"Our practice was very successful with trabeculectomy, and a pioneer in the use of antimetabolites, but I was troubled by the long-term risk profile," he continues. "The risk was incrementally small—but when it hit, it could be devastating. So, after being an innovator and enthusiast for trabeculectomy for most of my career, I walked away from creating blebs. Now I haven't done a bleb-based surgery for at least five years.

"I'm not saying that trabeculectomies shouldn't be done at all," he notes. "Some of my colleagues get very good results, and they should continue to do them. But more globally, my concern is that we're leaving people with filtering blebs that are at ongoing risk for trauma and endophthalmitis. I think the continuing risks of trabeculectomy, and our improved understanding and techniques for using tube shunts, have helped change people's perspective and may account for the gradual shift away from trabeculectomy to the increased use of tube shunts.

"I think those taking care of glaucoma patients need to keep the bigger picture in mind," he concludes. "We need to consider the impact on quality of life and the risk of catastrophic events when performing surgeries that create blebs. There are many ways to make a trabeculectomy safer, such as laser suture lysis, positioning and so on. But at the end of the day, we're still creating an opening—a potential passageway for bacteria from the surface to the inside of the eye—in tissue that's been

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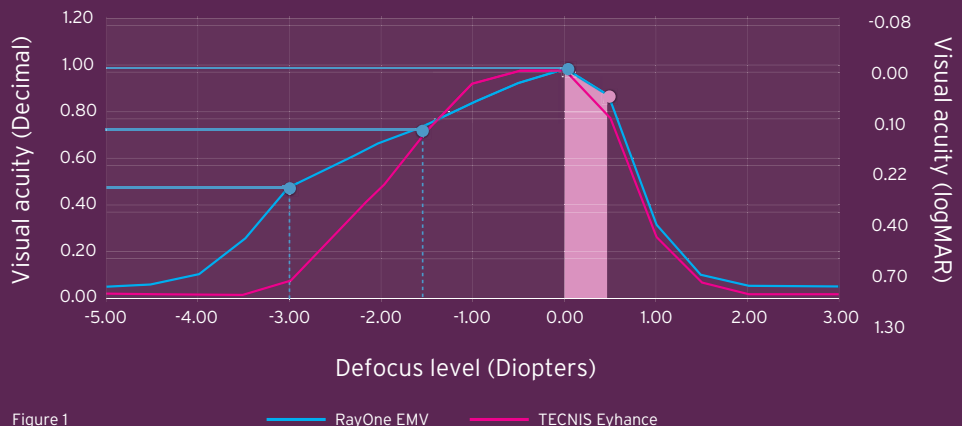

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subjected to glaucoma drugs for years, and often on top of mitomycin exposure at the time of surgery. I don't see an easy fix to the long-term bleb-related risk. In many cases, we get away with it. But in a few cases, it's catastrophic."

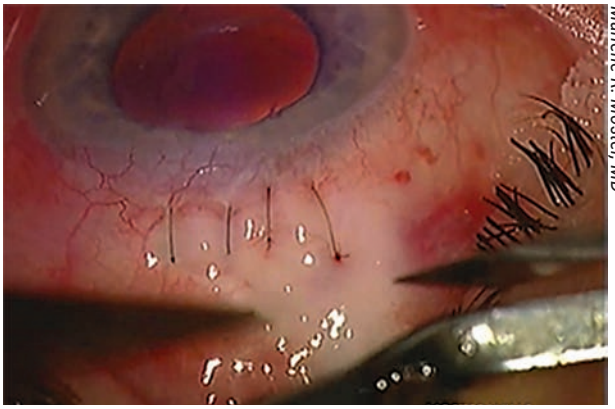
However, many surgeons have reservations. Dr. Moster says she doesn't find tubes to be an ideal first choice. "Very few tubes are totally successful on their own—meaning no glaucoma medication, no complications or decreased vision," she says. "If you look at the five-year treatment outcome of the Ahmed versus Baerveldt comparison study,[8] the number of complete successes at five years was nine (8 percent) in the Ahmed tube group and 14 (14 percent) in the Baerveldt tube group (p=0.27). That's not optimal.

"For me," she continues, "the biggest issue with tubes is that once they fail, the superior conjunctiva is limited, often requiring a second tube to be placed inferiorly. That's why I prefer a superior trabeculectomy. If the trabeculectomy doesn't work, I can needle it with mitomycin-C; and if that still doesn't work, the patient can always get a tube. Nothing is lost.

"I do regularly implant tubes in uveitic patients, some pseudophakes, those patients who work in sub-optimal environments, and older people who live far away," she notes. "Every patient has to be treated as a unique case."

Dr. Moster adds that in recent years she's tried to substitute MIGS procedures in as many patients as possible to decrease complications. "Unfortunately, MIGS doesn't always produce low enough IOPs," she says. "Patients with real glaucoma often end up back on medications."

"In the long run, some ophthalmologists may choose to do more tube shunts than trabeculectomies because the postop care is easier," notes Dr. Razeghinejad. "However, I'm not sure it's safer for the patient. If you do a shunt and it fails in two years, and the patient is young and phakic, what else can you do? You need to put another one in in a different quadrant. If you do a trabeculectomy and it fails in two years, you can put in a tube and you have a few more years for it to work. But if you do the tube first, it may be impossible to go back and do a trabeculectomy later."



Marlene R. Moster, MD

Full-thickness trans-conjunctival sutures can be used to treat hypotony.

Dr. Razeghinejad adds that the range of corneal complications with tube shunts is much greater than with trabeculectomy. "When we do a tube shunt, we need to consider the long-term complications," he explains. "If you do a tube shunt on a 45-year-old patient and see the patient for four years, you may not see a problem in the cornea. But if you follow that patient for 15 years, the cornea may eventually fail and the patient may need a corneal transplant. On the other hand, if you do a trabeculectomy and it works for 10 years, the likelihood of needing a corneal transplant is very low."

Dr. Razeghinejad notes that the reason for this longer-term risk with tube shunts isn't completely clear. "We understand why the cornea is at risk if the tube is touching the cornea," he says. "But in those patients where the tube isn't touching the cornea, we still see endothelial cell loss. It may be just because we're leaving a foreign body inside the anterior chamber. However, some people hypothesize that the convection inside the anterior chamber changes when you have a tube in there. It's believed that the aqueous produced by the ciliary body goes through the pupil and then flows downward to the inferior angle and then up to the superior angle. When we place a tube in the superior angle, the aqueous that's produced by the ciliary processes passes through the pupil and then goes directly into the tube. This change in the aqueous convection may have a negative impact on the corneal endothelial cells. This is just a hypothesis, but it seems reasonable." ◂

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OCTA IN THE RETINA: AN UPDATE

Experts discuss the pros and cons of optical coherence tomography angiography when compared to conventional dye-based angiography.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Optical coherence tomography angiography is a convenient and noninvasive way to identify and follow retinal and choroidal vascular pathologies by providing cross-sectional and three-dimensional images. However, despite these benefits, more work needs to be done before OCTA can be used in all patients, according to experts.

"OCTA has been around for several years," says David Boyer, MD, who is in practice in Los Angeles. "Its acceptance in the community is growing, partly because earlier versions of OCTA had many artifacts that made it difficult for the average ophthalmologist to interpret. Manufacturers have worked at reducing the artifacts, and I view the OCTA as a valuable asset in our armamentarium for examining patients. However, its place is still being worked out, regarding which patients should have it and when."

Here, physicians experienced in using OCTA discuss its strengths and limitations.

Understanding the Options

For decades, dye-based angiography has been the standard clinical imaging modality for evaluating retinal and choroidal vascular pathologies. Unfortunately, fluorescein and indocyanine green angiography are invasive and time-consuming. Additionally, fluorescein angiography is only two-dimensional and is unable to visualize the deeper capillary structures. Indocyanine green angiography is used mostly to image the choroid.[1,2] Because of these limitations, researchers have been studying faster, safer imaging tools that are capable of effectively imaging both the retinal and choroidal circulations.

OCTA makes it possible to study the hemodynamics of individual retinal and choriocapillaris vascular layers noninvasively. A recent review found that OCTA is a useful modality for evaluating retinal and choroidal blood flow in patients with inherited retinal diseases, including retinitis pigmentosa, Stargardt's disease, Best vitelliform macular dystrophy and choroidemia.[3] OCTA imaging has yielded new insights into the occurrence of vascular insufficiency in these conditions. Using OCTA to study retinal and choroidal blood flow in patients with inherited retinal diseases and dry macular degeneration may reveal further insights into the pathogenesis and natural history of disease in these conditions. The currently available OCTA units in the United States are the Spectralis OCTA from Heidelberg, Optovue's Angiovue and Zeiss' AngioPlex.

According to Dr. Boyer, the main benefit of OCTA is that it can be applied earlier and in a noninvasive way to monitor disease progression. "Much of this information can be obtained from the fluorescein angiogram, but that's an invasive test that would need to be repeated," he says. "OCTA has no radiation. It helps correlate the vascular changes that are occurring before we're able to visualize them. So, we will have more information on the disease process, basically."

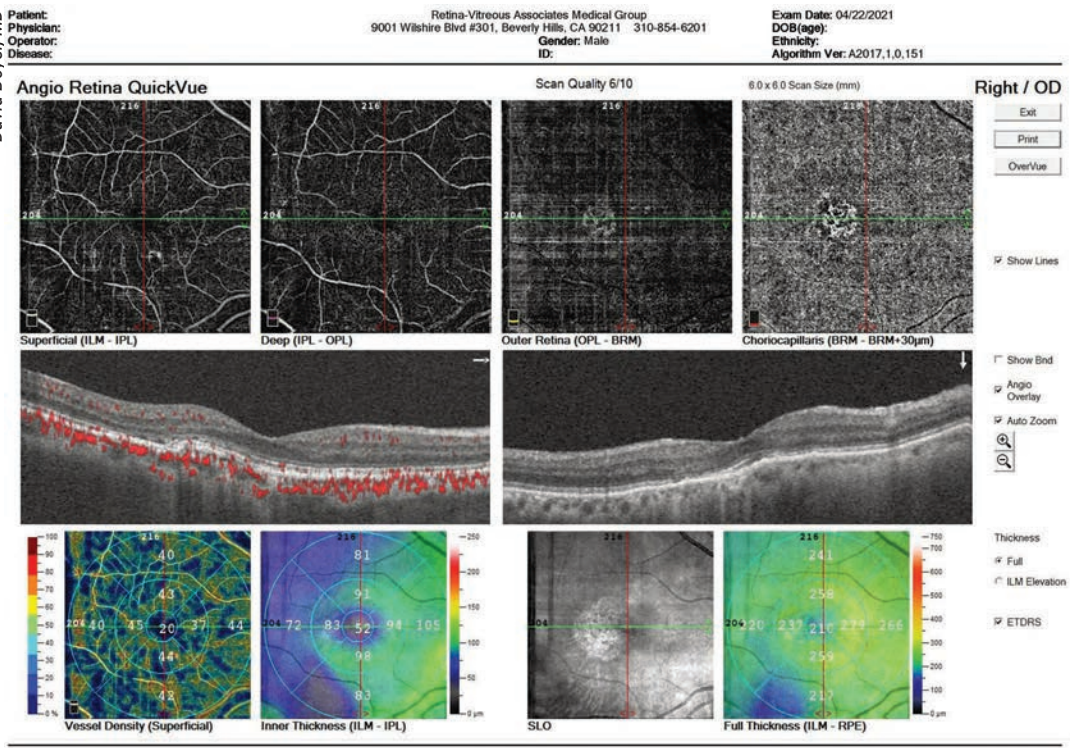
He adds that the use of OCTA has become more commonplace, and it

This article has no commercial sponsorship.

Drs. Boyer, Lim, and Stone have no relevant financial interests to disclose.

is used for a variety of conditions. "It's used for macular degeneration," he says. "Using OCTA, we can identify drusen that have become vascularized, which we could not do before. We can also see nonexudative choroidal neovascularization. Fluorescein angiography doesn't allow us to see those things."

Jennifer I. Lim, MD, director of the Retina Service at University of Illinois Health, adds that speed is a benefit of OCTA over fluorescein angiography. "Additionally," she says, "it provides 3D spatial localization, so you can see the different layers of the blood vessels, including the choroid, with the available segmentation layer analyses, without overlying vessels, unlike with fluorescein angiography. On fluorescein angiography, the vascular layers are matted on top of each other, so there are overlays. And, because OCTA is noninvasive, it's safer; you don't have to worry about allergic reactions to fluorescein dye. It is also helpful for imaging children and people with poor venous access."



David Boyer, MD

A choroidal neovascular lesion. Physicians say that optical coherence tomography angiography can be useful in such cases because they're able to see the choroidal neovascular membrane despite the presence of overlying retinal leakage that would obscure its presence on a fluorescein angiogram.

Dr. Lim says OCTA is helpful in particular conditions. "Today, OCTA is useful for identifying choroidal neovascularization," she says. "If you see the CNV vessels, you know it's there, and you don't have to do fluorescein angiography. It's also nice for follow-up on these patients to see the size of the choroidal neovascular membrane. A second useful indication is to clearly see the abnormal neovascularization of the retina in diabetes.

"It's also really useful when there is a disease that causes a lot of retinal vascular leakage and you're trying to determine whether there is an underlying choroidal neovascular membrane," she continues. "These situations occur when there is central serous chorioretinopathy or uveitis. The OCTA is useful because there's no leakage seen from the retinal vasculature, so you can visualize the underlying vessels in the OCTA image. You can see the choroidal neovascular membrane despite the presence of overlying retinal leakage that would obscure its presence on a fluorescein angiogram."

However, OCTA is not without its drawbacks. The images obtained are sometimes blurred and difficult to interpret. "For some images, it may be difficult to know what's noise or artifact versus what's real pathology," Dr. Lim says.

According to Thomas Stone, MD, in practice in Louisville, Ky., most OCTA units don't provide the same amount of information as dye-based angiograms. "In other words, you receive information about a smaller area, and it doesn't show leakage," he says. "It just shows where vessels are open and if there are new vessels, but it doesn't tell you if the vessels are leaking. It's not a dynamic view like fluorescein angiography."

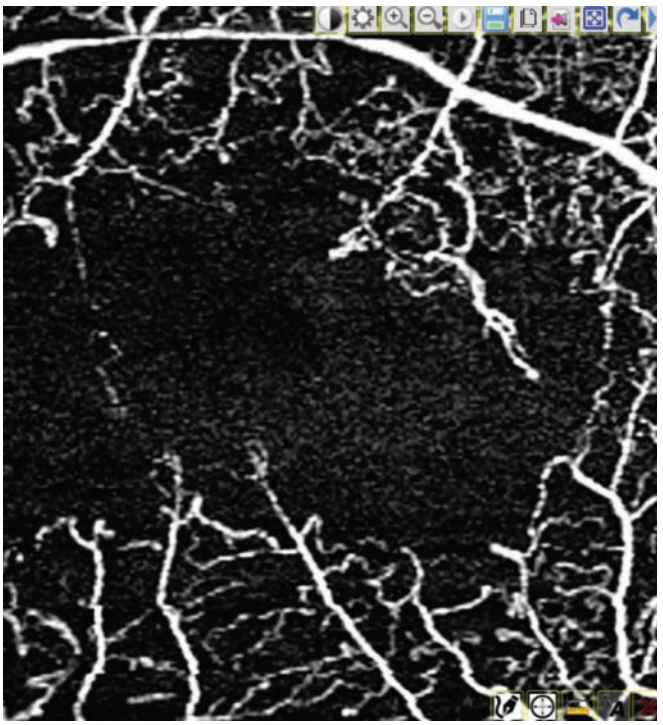
Additionally, it hasn't yet been determined when OCTA should be used and in which patients. Dr. Stone uses it for his patients with retinal vascular disease and in diabetic patients if they have edema or if their vision has decreased. "It gives me an idea of what their visual potential will be if I give them injections," he says. "Additionally, for patients with retinal vein occlusions, I can gauge the amount of ischemia, and that gives me a sense of how much treatment the patient will require. I also use it in choroi-

dal neovascular disease."

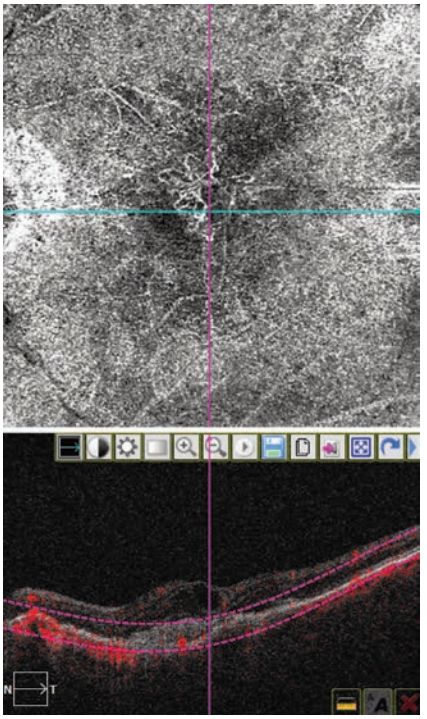
Swept-source OCTA offers a wider field of view and can be a valuable tool. "However, this is a specialty item that many people don't want to invest time and money in," notes Dr. Stone. "I don't think OCTA will ever fully replace traditional angiography, because I think there's still a role for evaluating the leakage."

He says that, while the use of OCTA is currently not critical, it is helpful. "If I end up in a clinic without it, it's not like I can't take care of patients; however, there's definitely a subset of patients in whom it can help you make more informed decisions about whether to treat them and how to treat them," he says. "It's not currently standard of care, but it certainly makes your care better and more thorough in the subset of patients who need it."

Thomas STone, MD



A 3x3 macular image on OCTA.



An 8x8 image of the macula on OCTA.

Research and Artificial Intelligence Applications

In addition to clinical applications, OCTA has research and artificial intelligence applications, says Dr. Lim. "Our group is working a lot on artificial intelligence applications to use OCTA for diagnosis of retinal conditions such as sickle cell diabetic retinopathy," she says. "We've shown that you can actually use OCTA, and that the sensitivity and specificity are pretty high based on quantitative parameters."

A recent study conducted by Dr. Lim and her colleagues found that artificial intelligence classification is a promising novel and affordable screening tool for clinical management of ocular diseases.[4] The study included an OCTA image database of 115 images from 60 diabetic retinopathy patients (20 mild, 20 medium, and 20 severe cases of nonproliferative diabetic retinopathy), 90 images from 48 sickle cell retinopathy patients (30 patients had stage II mild and 18 patients had stage III severe sickle cell retinopathy) and 40 images from 20 control patients. There were no statistically significant differences in age and gender distribution between the three groups. In patients with diabetic retinopathy, no significant difference in hypertension or insulin dependency between stages of disease groups was observed.

They used a logistic regression-based model with backward elimination to select the optimal combination of features for the multi-task classification. Blood vessel tortuosity, blood vascular caliber and foveal avascular zone parameters increased with disease onset and progression, while blood vessel density and vessel perimeter index decreased. The backward elimination initially started with all OCTA features and eliminated features one by one based on the prediction accuracy of the fitted regression model. The feature selection method identified an optimal feature combination for each classification task.

The support vector machine classifier performed the classification tasks in a hierarchical manner. Then, the investigators measured the sensitivity and specificity task to evaluate the diagnostic performance in each task. The receiver operation characteristics curves were drawn, and the area under the receiver operation characteristics curves were calculated for each task. At the first step, the support vector machine distinguished diseased patients from control subjects with 97.84-percent sensitivity and 96.88-percent specificity. After identifying the patients with disease, the classifier sorted

(Continued on p. 85)

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BIG DATA AND OPHTHALMOLOGY, 2021

Being able to compile and analyze huge quantities of real-world data is having a significant impact on practice.

CHRISTOPHER KENT
SENIOR EDITOR

As we move into the digital era, a host of new technologies (and the problems and advantages that accompany them) continue to appear. As part of this unfolding story, the evolution of electronic health records has led to the possibility of collecting and analyzing enormous amounts of data—and as people have begun exploring this possibility, large databases of information have begun to spring up.

Here, people with extensive experience with two of the current databases in the United States—the American Academy of Ophthalmology's IRIS (Intelligent Research In Sight) Registry, and the Vestrum database, currently working exclusively with retina specialists—share their experience, discuss the pros and cons of these systems, and offer their thoughts on where this technology may lead us in the future.

The IRIS Registry

"The IRIS Registry started in 2013," notes Flora Lum, MD, vice president of Quality and Data Science for the AAO since 2015. (She leads the Academy's quality of care programs and the teams that are responsible for clinical guidance, public health and data analytics initiatives, including the Academy's IRIS Registry.) "As of April 1st 2021, about 3,000 practices are contributing their EHR data to the database; we have data on 68 million unique patients and 387 million visits. The majority of practices in the United States are participating, and we believe our data includes the majority of eye-care patients in the U.S." (Participating in the Registry is free to members of the Academy.)

The Academy has partnered with other companies to help manage the massive amount of data the IRIS Registry brings in, as well as potential commercial applications for that data. Currently, the Academy is working with Verana Health, a company with offices in San Francisco, New York City and Knoxville, Tenn.

Mark S. Blumenkranz, MD, MMS, H.J. Smead Professor of Ophthalmology, Emeritus, at Stanford University, CEO of Kedalion Therapeutics and a director of Verana Health, explains that Verana helps to manage the enormous amount of data collected by the registry, in a number of ways. "Data collection is a complex operation," he says. "Even though most of the relevant data now resides within EHRs rather than paper records, it's not as simple as just pulling it out and sticking it into a computer algorithm for compilation and analysis. Data needs to be curated to be certain it's accurate and reproducible.

"For instance, sometimes data entered into an EHR is misclassified," he explains. "You have to have mechanisms by which you can ensure that the data being extracted is of good quality—that the fields were filled out properly. If you don't curate the data, it's essentially worthless, or at least of limited value. But data curation takes time, and it's expensive.

"How quickly the data is processed is also an issue," he continues. "For example, if you're looking at trends in drug treatment and you identify a potential problem with a drug, you need to get the data right

This article has no commercial sponsorship.

Dr. Blumenkranz is a director at Verana Health. **Dr. Williams** is a cofounder of Vestrum Health. **Dr. Lum** is Vice President of Quality and Data Science for the American Academy of Ophthalmology. **Ms. Huskins** report no financial ties to any product discussed in the article.

away. You need to have automated extraction routines and connections between the servers and the data repositories."

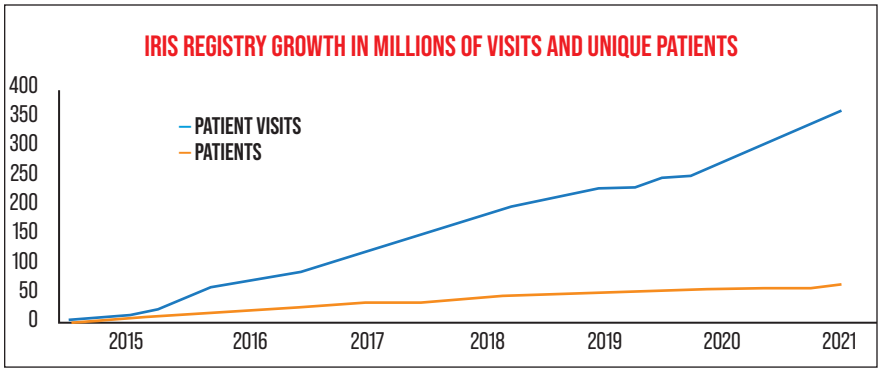
Users in the field report a positive experience with the IRIS Registry. "We started using the IRIS registry when they first created it," says Michele Huskins, EHR specialist at the Rocky Mountain Eye Center in Pueblo, Colorado, a practice currently employing 21 ophthalmologists and optometrists. "For us, it's been great. I think the reporting is much better than what I can get from my EHR. For example, I can pull up reports listing patients who do or don't meet a given measure. I can also open tickets and go back and forth with staff members."

Ms. Huskins says that being part of the registry is very easy. "It takes all of the data right out of our database," she notes. "I just look at the dashboard, which they update once a month, and pull reports on the things I'm concerned about. It's very user-friendly.

"What's really nice is that the system will map custom fields like those we've created in our EHR system, to give us the data we need," she continues. "They take screen shots of our templates. For example, we have custom templates for patients who are converting to cataract surgery, and we've created some custom fields like the surgeon's planned refraction. We're currently working with the IRIS registry folks to map those fields, so whatever our doctors put in about how close the patient came to the planned refraction, they can pull up later as part of a report.

"The registry folks also make sure the database is capturing the pre-existing fields in which we enter information we need," she continues. "In contrast, sometimes the EHR's workflows are not very user-friendly—we have to do a lot of clicking to get to the data we need."

One of the most popular—and practical—ways in which the IRIS Registry helps practices is by generating the reports that practices are required to submit to comply with Medicare quality-of-care standards. "Over the past five years," Dr. Lum says, "our quality reporting has helped practices avoid more than $1 billion in penalties relating to Medicare's Merit-based Incentive Payment System [MIPS], as well as helped practices achieve small bonuses every year."



"Creating those reports is a big burden to physicians," Dr. Blumenkranz points out. "It takes a significant number of people and amount of technical expertise to generate them. The partnership between the AAO and Verana is sort of a perfect synergy in this respect."

Vestrum Health

Another data registry in the United States is Vestrum Health, which currently works only with retina specialists; it was also started in 2013. "The Vestrum database is able to acquire HIPAA-compliant, de-identified data directly from a practice's EHR, without any effort from the physicians themselves," explains David F. Williams, MD, MBA, a partner at VitreoRetinal Surgery in Minneapolis/St. Paul, and cofounder of Vestrum Health. "We specify the data fields that are valuable—the ones that can provide actionable data—and then we aggregate the data from each practice into an analyzable database. The database contains all of the historical data for the practice, and it's updated on a weekly basis; it can be queried and analyzed to answer almost any clinical question a doctor may have.

"We're currently working with about 15 to 20 percent of the retina specialists in the United States," he says. "That's a meaningful percentage because the practices participating are representative of retina as a whole, in terms of their geographic distribution, size and other characteristics. People don't pay to participate; Vestrum provides data and analysis that's valuable to practices in exchange for access to the EHR data from them. We've also done projects for industry.

"With today's EHR systems, it's very complex—or even impossible—for a practice to try to pull data out in any organized, analyzable fashion," he continues. "But with Vestrum, if participants want to do a research project or look at some aspect of their own practice, they just have to let us know and we can do it with them."

Dr. Williams says Vestrum provides participating practices with a standardized monthly report called QuickTrends, showing the practice's data. "It's secure, de-identified and HIPAA compliant," he notes. "It allows you to analyze different aspects of your practice—the volume of different procedures, outcome trends, realizations of drug treatments, and so forth. Vestrum is now developing a version of the report that includes a searchable database containing all of the practice's EHR data over time."

Dr. Williams says that Vestrum's relatively small size is both an advantage and a disadvantage. "The

feedback we get is that the Vestrum system is very user-friendly, partly because of our smaller size," he notes. "It's easy to make changes on the fly, and easy to get in touch with the people providing data to you. That makes it easy to adjust the data you're seeing, refine the questions you're asking and drill down to the answers you're really looking for."

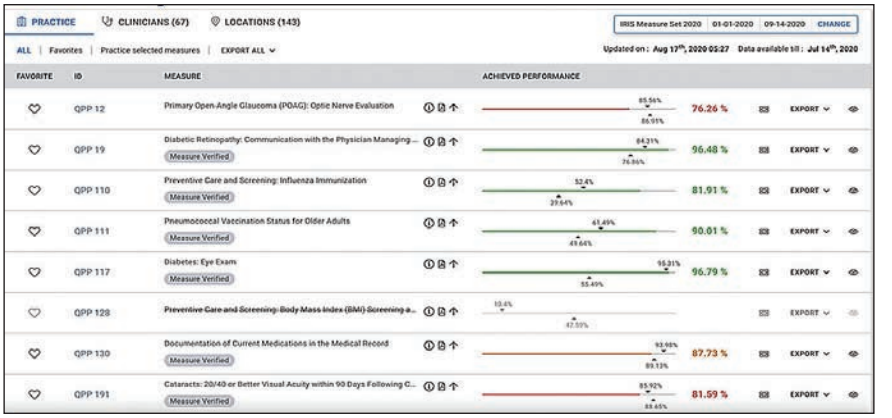
Dr. Williams admits, however, that Vestrum's size is also something of a disadvantage. "We'd like to grow the panel of physicians who contribute to our database, in part because we don't have the same power that a large organization like the American Academy of Ophthalmology has," he says. "We can't compel the EHR databases to provide their data to us for free, so we pay the EHR providers to make the connections for us. We ask our practices to encourage their EHR provider to not only provide the data but provide access to more data fields so that we can do even more nuanced investigations."

Practice Benchmarking

There's no question that practices can benefit from being able to do both external comparisons—how the practice is doing compared to other similar practices—and internal comparisons, revealing how different branches of a practice, or individual doctors, are doing compared to the others.

"We provide two types of benchmarks, one based on data from CMS for all reporting through MIPS, and one based on everybody who reported to us," explains Dr. Lum. "We report the data for the ophthalmologists in the registry, and data for optometrists and other clinicians, depending on the type of measure in question. So a practice can see how it's doing overall, and how it's doing within the IRIS Registry.

"In addition, doctors can look within their own practice and compare different staff members and different office locations," she continues. "They might find a noticeable difference between two locations; if so, they can try to figure out why the workflow or documentation is different here than there. In essence, the data allows them to look at the quality they're delivering and helps them manage it."



A sample IRIS Registry dashboard relating to practice quality measures. (© *FIGmd Inc 2021. All rights reserved. No reproduction in any form without prior permission from FIGmd*.)

Dr. Lum notes that doctors can drill down to individual patient data. "We like to give what we call 'actionable feedback,' " she says. "Saying that 20 percent of your patients didn't meet a measure doesn't help you much. With this data you not only can see that one particular patient didn't meet the measure, you can also go back into your EHR system and see if the surgeon didn't document something, or whatever else the explanation might be.

"A practice can make adjustments to its workflow, or call patients to get them to come back, or send a report to the referring specialist," she continues. "It all depends on which measure they're looking at. Practices can screen for different patient characteristics, such as use of tobacco or comorbidities, and use that data to evaluate their patient population and risk factors. You can look at all of your glaucoma patients and see how they're doing with IOP control, or look at your diabetic patients and see how many have had a letter sent to their primary care physician. It's a very extensive and detailed program."

Dr. Lum notes that access to this data is also timely. "Normally, when you report for MIPS, you don't get your performance and follow-up data until about a year and a half later," she points out. "In the IRIS Registry, every practice has a dashboard that's refreshed with new data every month."

Ms. Huskins says her practice takes advantage of the benchmarking capabilities. "I compare our practice to the rest of the country," she says. "For about half of the measures, we're above the national average. I look at reports showing patients who are not meeting a measure, and then look for the reason. That helps us know what we need to improve on. It's definitely giving us information that we can use.

"I also do a little bit of comparing within the practice, doctor to doctor," she adds. "Often that alerts me to a mistake in our data capture; if one doctor's numbers are very low, I know it's an issue with our data capture and I can do something about it."

Ms. Huskins says this kind of data analysis has led to practical changes. "For example, each day I automatically create a report in our EHR that shows me all the people who came in yesterday with a diagnosis of diabetic retinopathy," she says. "Then, I check each patient's chart

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to make sure that we've sent a letter to the primary care physician. If not, I send a note to the tech to take care of that. Later, if the diagnosis says that the patient no longer has retinopathy, I send the tech a task to remove that from the patient's chart, so the patient is no longer part of the denominator for that measure. Without the IRIS system, we couldn't manage this as easily."

Dr. Williams says having access to Vestrum in his own practice has made a significant difference. "It gives us an awareness of what's happening on a larger scale, rather than just basing our judgments our own day-to-day experience with patients," he notes. "For example, it's allowed us to look at some of our outcomes using different drugs. Because of what the data has revealed, we've made some mid-course corrections in practice activities. Being able to quickly look at trends in our patient numbers, treatment numbers and utilization of various pharma products—without having to query someone in our business office—has been very helpful."

Assessing Real-world Impact

Another key use for large databases of real-world information is monitoring what actually happens when a drug, device or even a new technique comes into common use.

"After a device or drug gets approval, you still have to commit to doing research to see what happens in the real world," says Dr. Lum. "We have a natural surveillance system that can detect adverse events, such as adverse ocular effects arising from a systemic drug. Doctors and practices are too busy, or simply forget to file formal adverse effect reports, even though those systems are in place. Our data can help companies and the FDA look at early warning signs of any issues that come up. With so many patients in the database, we can spot them before anyone else is likely to."

Dr. Blumenkranz agrees. "One key thing this data can do is provide information about what's currently happening, such as timely estimation of the incidence of different diseases, and how good the results of specific treatments are," he says. "The data coming out of the IRIS registry, once it's been curated and analyzed, provides real-world evidence for assessing the safety and efficacy of any number of different types of interventions: drugs; devices; public health measures; and so forth."

For example, a 2020 study used the IRIS data to compare the effectiveness of treatments for 13,410 treatment-naïve patients newly diagnosed with diabetic macular edema who were seen between July 2013 and March 2016.[1] It found that:

WILL BIG DATA REPLACE CLINICAL TRIALS?

Given that a large database can show real-world outcomes of different treatments, it's reasonable to wonder how this might affect the conduct of clinical trials in the future. Recently, Verana Health was able to use real-world data from the IRIS Registry to replicate the primary outcome measures of the VIEW I and VIEW II clinical trials. (Those trials led to the 2011 U.S. Food and Drug Administration approval of aflibercept [Eylea, Regeneron] for the treatment of neovascular age-related macular degeneration.)

In this registry-based retrospective study, the inclusion and exclusion criteria of the VIEW studies were applied to patients whose data were part of the IRIS Registry; 4,779 patients were found whose disease and treatment were comparable to the 1,632 subjects in the trials. Matching the treatment times, the proportion of eyes losing fewer than 15 letters among the IRIS Registry patients was similar to that found in the VIEW studies, indicating proof-of-concept. This was the first time a real-world dataset was able to replicate the results of a large randomized, controlled clinical trial.

"This type of data differs from the data produced by prospective, randomized clinical trials in some fundamental ways," notes Mark S. Blumenkranz, MD, MMS, H.J. Smead Professor of Ophthalmology, Emeritus, at Stanford University, and a director at Verana Health. "The clinical trial data can provide a lot of insight into whether a drug is effective or not. But how these drugs end up being used in the real world is a huge concern. Maybe the frequency of drug administration is different; maybe the dosing is different. The real-world data gives us a much better idea of how the drug functions in real-time clinical practice."

"Unfortunately, using the database in this way doesn't always work because the patient characteristics may be hard to duplicate," notes Flora Lum, MD, Vice President of Quality and Data Science for the AAO, who works with the IRIS Registry. "We tried to do this to confirm the results of one small glaucoma study, and we weren't able to replicate the clinical trial results. We couldn't find patients that neatly fit the categories used in the randomized, controlled trial, and some of the technology and practice patterns had changed since the study was done. But in the more recent attempt [described above], we were able to replicate the patients in the study more successfully."

Dr. Lum says she doesn't believe a large database like the IRIS Registry will ever allow researchers to skip doing clinical trials. "The registry provides observational data," she notes. "We can't provide strict controls and we can't prove causality. It might be possible to use the IRIS Registry as a mechanism to collect the data for a randomized, controlled trial, but real-world evidence isn't the same as randomized, controlled trial data, which is level-one evidence because of its strict protocols and controls.

"On the other hand, we can use the IRIS Registry to see if what happened in a randomized controlled trial actually does work in the real world," she continues. "The database could be an adjunct that can help to reinforce what we learn and then also raise questions. It might reveal, for instance, that because of trends or changes in practice patterns, a given study's results may no longer apply in the real world."

—CK

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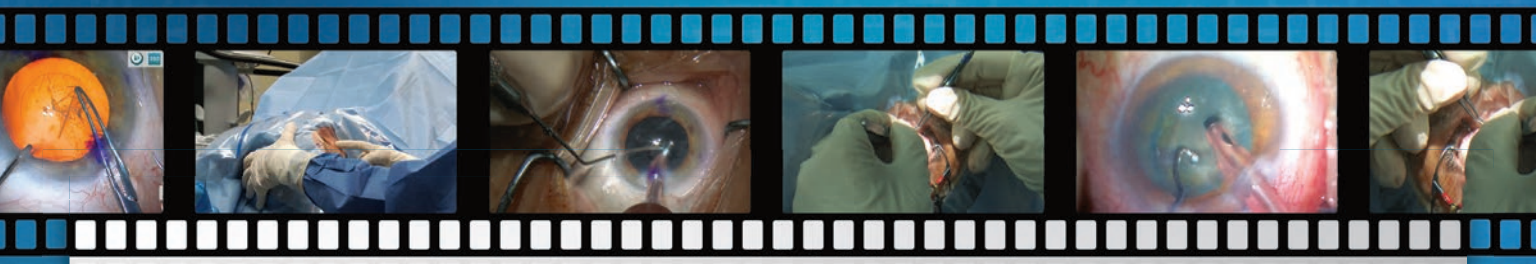

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— 74.5 percent of patients received no treatment within 28 days of diagnosis.

— Within the first year, 3,155 (24 percent) were treated with anti-VEGF injections; 1,841 (14 percent) received laser; 239 (1.8 percent) were treated with steroids; and 81 (0.6 percent) received a combination of two or more treatments.

— Among patients receiving anti-VEGF injections, 71.3 percent were treated with bevacizumab, 17.1 percent with aflibercept, and 11.6 percent with ranibizumab.

— Patients who were treated within the month following diagnosis had greater initial visual impairment than those not treated during month one, and achieved greater levels of visual acuity improvement at one year.

Dr. Blumenkranz notes that this kind of data can also reveal rare side effects only evident when large number of patients are exposed to a treatment. "In fact, there was at least one recent drug introduction where a very infrequent but very serious complication was identified subsequent to approval," he says. Dr. Williams says Vestrum's data has also shown that real-world outcomes can diverge from the outcomes in pivotal clinical trials, including in the trials that led to the approvals of different anti-VEGF agents currently in use.

This type of real-world monitoring can also be used to assess the value of a new surgical technique, or to compare the outcomes of different surgical options. "Doctors often have questions about whether one technique produces better results than another," Dr. Blumenkranz notes. "In most cases, no one is going to conduct a clinical trial to resolve this; most of the time you can't do a large enough trial, for ethical and practical reasons, to be adequately powered to get an answer. Even when people have tried, the results have often been inconclusive.

"On the other hand, if you look at the data from more than 1,000 retinal surgeons, you'll see that some do things one way, some do things another way," he continues. "Based on their outcomes, even though you're not randomizing, the numbers are large enough that you should be able to derive some degree of statistical significance around the differences in outcomes using retrospective data, if appropriate methods of matching are employed. It's essentially an alternative to a prospective, randomized clinical trial.

> **In the long run, big data in health care is going to have tremendous value.**
>
> ***—David Williams, MD, MBA***

"The conclusions aren't as indisputable," he admits, "because you can't ensure that the patients in one group are identical to the others; but if you start with very large numbers, you can create pretty comparable groups in terms of their baseline characteristics. From that you can work backwards to conduct a sort of synthetic trial, where you have patients randomized to multiple groups post-hoc."

The data has also been used to demonstrate how potential changes could improve things like systemic health-care costs. A study published in 2020 used data from the IRIS Registry, together with Medicare claims data, to demonstrate that a 10-percent increase in bevacizumab market share relative to ranibizumab and aflibercept would result in Medicare savings of $468 million and patient savings of $199 million. This could be triggered by increasing the reimbursement for bevacizumab to equal the reimbursement for aflibercept, eliminating the financial disincentive responsible for the limited use of bevacizumab.[2]

Moving Ophthalmology Forward

Being able to access great quantities of real-world data is also having an impact on the field as a whole, via a number of data uses:

• ***Providing data for research reports.*** "Verana Health is helping to create the research reports that are being published by the Academy, using the IRIS database to detect trends and answer questions," says Dr. Blumenthal. "The partnership enables the data to be of very high quality, including providing statistical support."

For example, a study of endophthalmitis occurring within 30 days of cataract surgery in the United States, based on IRIS Registry data for 8,542,838 eyes that underwent the surgery between 2013 and 2017, was published in 2020.[3] Among other things, the data revealed that: 3,629 eyes developed endophthalmitis (0.04 percent); the incidence was highest among patients 17 years of age and younger (0.37 percent over five years); endophthalmitis occurred four times as often following combination surgeries, compared to standalone surgery; and 44 percent of patients who developed endophthalmitis still achieved 20/40 or better visual acuity at three months.

• ***Helping to guide researchers working on developing new drugs.*** "When you're trying to develop new drugs, one issue is deciding which diseases to treat," Dr. Blumenkranz points out. "With registry data, you can find out the number of patients with a given health problem who are being seen, whether they're being treated, and what the clinical outcomes are. Based on that, you can come up with a list of the most common diseases and which ones we have good treatments for. Then you can tailor your drug discovery process to diseases that are frequent but have limited treatment options."

• ***Recruiting patients for trials of rare disease treatments.*** "If a disease is encountered infrequently, as with

orphan diseases, the number of affected patients can be small and clinical trial recruitment can be challenging," Dr. Blumenkranz notes. "No single center will have a large number of those patients that you can quickly enroll. The registry data gives you an overview of the large-scale epidemiology.

"Another way Vestrum is helping practices is by enhancing their recruitment into current clinical trials," says Dr. Williams. "If a practice wants to avail itself of our clinical trial service, we can look at the eligibility criteria for a particular trial and then search the practice's database and generate a list of patients that might meet the trial's eligibility criteria. We can include patients that might have been seen even years ago. That's a list the practice itself might have a hard time compiling."

Dr. Lum also notes that the IRIS Registry might allow data to be collected for a clinical trial more easily. "If you can enroll patients from participating practices and then use the IRIS Registry to collect data," she says, "you could probably do a trial for less money, and quicker."

Adding Images to the Database

Something that all current databases are investigating is finding ways to include images in the database. "The optimal database should contain three things: the traditional EHR data, e.g., symptoms, signs, physical findings, and lab tests; medical imaging, which is particularly important in ophthalmology; and genomic data," says Dr. Blumenkranz. "If you have those three components, you have a pretty complete understanding of the patient.

"For example," he continues, "if you see somebody who has a complement-factor-H abnormality and also has a few drusen, you know that patient is at risk for vision loss. If you just saw that patient in the clinic and their vision was 20/20, you wouldn't necessarily have gotten a sense of the likelihood of that patient going on to more severe vision loss, or the optimal frequency of follow-up exams. Having the retinal image and genotype can be crucial.

"It's possible for the IRIS Registry and Verana Health to incorporate all three of these types of information," he notes. "Part of it is just a logistics issue; we have to get patient permission, practice permissions, determine who owns the data, and so forth. But it's not a particularly big deal to integrate those three things. However, getting the image data is currently a challenge due to issues of compatibility between different storage systems, as well as concerns about data ownership and privacy. Some EHR vendors are starting to incorporate images, but many practices use a separate vendor to provide storage for images."

Not surprisingly, analyzing the images to make them meaningful as data is an issue. "Up until now it's been extraordinarily labor-intensive to analyze imaging data," Dr. Blumenkranz says. "At reading centers people sit at a desk with a magnifier, and it's hard work. But an AI-enabled software package can analyze an image in milliseconds. So I think the ability to handle all of that data will become increasingly easy because of automated data ingestion and image analysis. Of course, people will have to decide the purpose of the analysis, and the software has to undergo training and validation and approval. But once that's done, the task will be dramatically easier and faster for a machine than for a person."

Dr. Blumenkranz points out that there are also security issues that may arise connected to including images in the database. "We'll need to have adequate protections for privacy," he says. "A fundus image is both protected health information and personal, identifiable information. A computer algorithm can tell from a fundus photo who you are—if the algorithm can match the photo to another image that's out there. It's like the debate over whether facial recognition software should be used on the street. Some of the same questions apply to medical images. It's not an issue right now—but it could be in the near future."

"Being able to correlate what's showing up in the EHR with the image findings is the Holy Grail for a lot of research studies, and also for industry," says Dr. Williams. "However, I'm not sure anybody's been able to solve the practical problems at this point. Vestrum has been working on it for a while, and we know that we can do it. It's just going to require some significant resources and the commitment of practices that also want to get involved in this type of project."

Into the Future

Dr. Lum believes a database like the IRIS Registry will allow doctors to improve treatment. "Doctors have never had a tool that could let them look at all of their diabetic patients, for example, or all of their cataract patients," she says. "The findings of IRIS Registry analytics should help doctors make decisions about what treatments are best for which patients. And it can help clinicians understand disparities in care by revealing which patients get treatment and which don't, or why some patients are lost to follow-up. The data may also help to understand more quickly new treatments that are working well, which might help accelerate payer acceptance of those treatments in clinical practice."

In terms of the future, Dr. Lum sees the database helping to answer questions about when, and in which patients, a given treatment is likely to be effective. "Big data in concert with artificial intelligence could help doctors treat and diagnose better, because we have all of

(Continued on p. 83)

Variable Vision after Glaucoma Surgery

Even when the outcome appears to be good, patients may complain of vision problems. These steps will help.

SAHAR BEDROOD, MD, PHD
PASADENA, CALIF.

Glaucoma surgery is an essential tool in a glaucoma specialist's armamentarium. But sometimes—even when an outcome appears to be good and vision measures close to 20/20—patients complain that their vision isn't right. In many cases the complaint is triggered by fluctuating vision.

A number of issues can cause this type of complaint, including hypotony, refractive error, astigmatism from the sutures and surgery, a slow, chronic bleb leak, corneal folds, macular striae and inflammation. Here, I'll discuss the different problems that may be causing these vision issues, and offer some suggestions for managing them and making sure your patient ends up happy.

Refractive Changes

Sometimes what's disturbing the patient is a refractive alteration, such as a myopic shift or an increase in astigmatism. Sometimes—though not always—these changes are related to postoperative hypotony, which may occasionally happen despite our best efforts

• ***Myopic shift.*** One of the consequences of hypotony can be a myopic shift in the patient's refraction. The loss of intraocular pressure causes the anterior chamber to shallow, and the whole lens-iris diaphragm moves forward, leading to the myopic shift.

• ***Astigmatism.*** New postop astigmatism can cause your patient to perceive that "something is off" about their vision. Astigmatism can result from a number of possible causes:

—*Hypotony.* Hypotony alters the dimension of the eye; one of the consequences can be astigmatism.

—*Cautery.* If you're doing a tube or trab, you may find that you need to control a bit of bleeding, and you can use cautery to close off some of the leaking blood vessels. It's not uncommon for surgeons to do this along the limbus. Light cautery usually doesn't produce any unintended side effects, but if you have to do more heavy-handed cautery you can burn the collagen on the sclera, which can cause the tissue to shrink and pull on the anterior part of the eye. That can remodel the tissue, changing the shape of the sclera and causing astigmatism.

—*Sutures.* Intraoperatively you may place vicryl sutures that will dissolve, and the sutures can lead to temporary vision changes. The tighter the sutures are, and the closer to the limbus or cornea they are, the more likely they are to cause astigmatism. The key is to tell patients before any major glaucoma surgery that their vision can be affected for up to six weeks after surgery. That's how long the sutures will take to dissolve.

Postop, you can remove the sutures if there's good closure and no leaks. However, I'd wait three months before doing any permanent refractive correction.

Chronic Bleb Leak

Another possible explanation for post-trabeculectomy patients with 20/20 vision but a visual complaint is a bleb leak. Symptoms may include: decreased IOP; occasional tearing; occasional blurry vision; shifting vision quality; and/or the patient says that pressing on the eye causes a change in vision. Those are indications that you should do a fluorescein stain to check for a bleb leak.

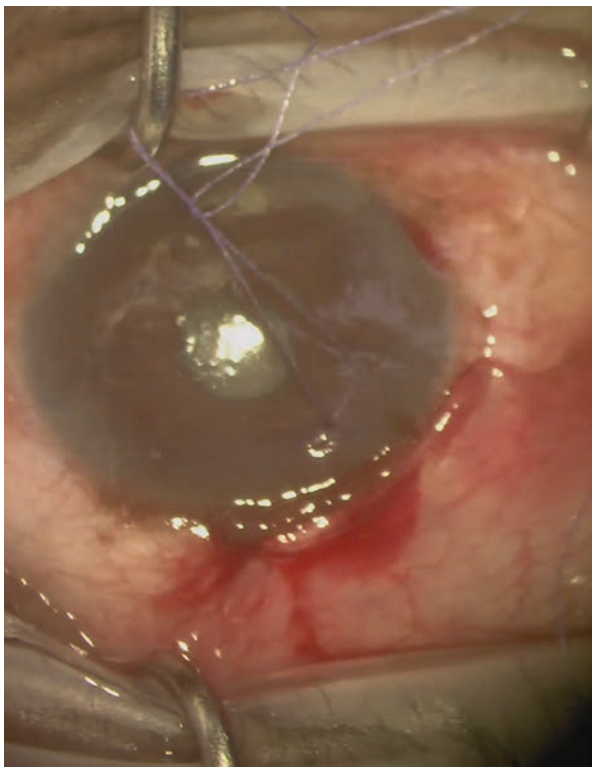
If I find a bleb leak early in the postop period, I may reduce the patient's steroids to increase the rate of healing. (This is somewhat controversial; every surgeon has a different idea about the best way to address this.) Usually when I cut back on the steroid I see the patient back in a few weeks and the bleb leak is gone. Of course, it's necessary to continue topical antibiotic coverage until the leak has stopped.

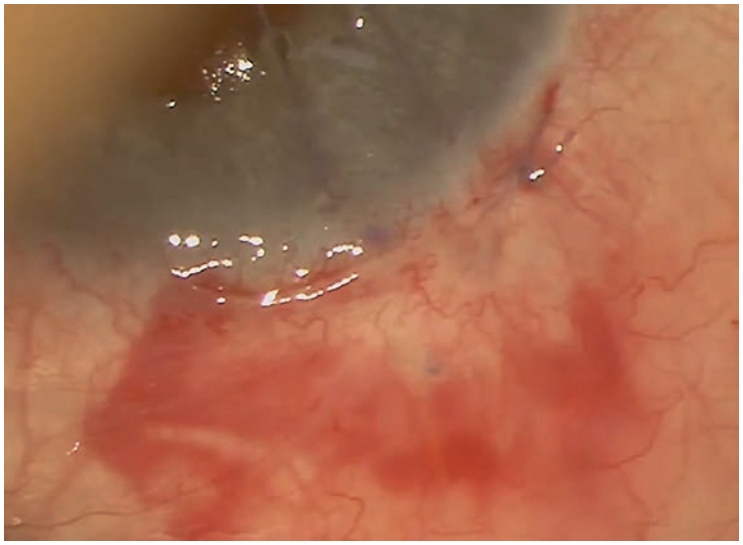
Occasionally a bleb leak is caused by the eyelid rubbing against the bleb; in that situation I'll put on a bandage contact lens to keep the lid from touching the eye. I've used pressure patches in the past; you roll up a patch and press it down on the eye so that the eyelid is stuck down and isn't rubbing against the wound. That has variable success.

When dealing with a bleb leak late in the game—three to six months postop or more—my advice would

This article has no commercial sponsorship.

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





Astigmatism caused by sutures can lead to postoperative patient complaints about vision. The tighter the sutures are, and the closer to the limbus, the more likely they are to cause astigmatism. Patients should be forewarned that vision may be affected by this for up to six weeks postop.

be to revise the bleb, because at that point it's not going to heal on its own. A bleb leak at this point usually means the bleb is cystic, or has a problem that's not wound-related. I take these patients back into the OR and revise the bleb. (Some surgeons attempt autologous blood injection, compression sutures, aqueous suppression and other techniques prior to bleb revision.)

Most times, when we revise a cystic bleb we cut into the bleb, remove the cystic tissue and then pull down healthy conjunctiva and suture it up. However, that doesn't always work; there's scarring all around the original bleb, and sometimes you simply can't pull the tissue down as far as you want.

One alternative, minimally invasive approach I've encountered was developed by Dr. Neeru Gupta, MD, at the University of Toronto.[1] She'll sometimes rotate the eye downward to expose the superior bleb; then she injects an anesthetic behind the bleb, causing the conjunctiva to balloon up to the outer edge. She then grasps the raised conjunctival tissue with 0.12 forceps and brings it down, using a 10-0 nylon suture to anchor the leading edge of the tissue to the limbus. This effectively covers the leaky area with healthy tissue.

Corneal Folds

Variability in vision can also be caused by folds in the corneal epithelium, another possible side effect of hypotony. If hypotony is present I always look for corneal folds, because hypotony can cause the cornea to contract. The resulting folds can be very subtle, but they can cause problems with the patient's vision over the long term. Placing fluorescein into the eye will reveal the edges of the folds.

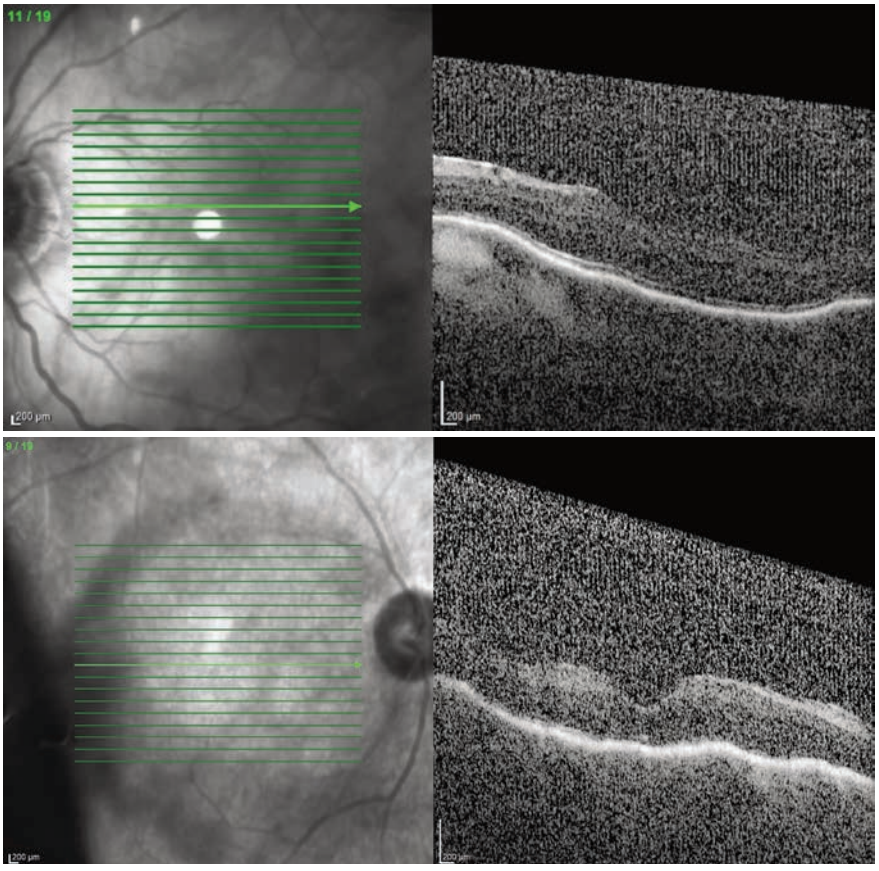
The treatment for this problem is to first of all determine what the cause of the hypotony is. Is it overfiltration? A leak? If necessary, revise the bleb. I also look into any glaucoma drops the patient may be using. I've seen many patients continue their drops postoperatively, even if their pressure is low; you have to get them to stop using any potentially IOP-lowering drops. If I know the patient is a steroid responder, I may also add a steroid to increase the IOP.

Hypotony Maculopathy

Variable vision can also be caused by hypotony maculopathy. For this reason, if a patient comes in and her vision isn't quite where I want it to be, I get a macular OCT and look for striae. Usually this problem is symptomatic, meaning that the patient isn't 20/20. However, I've been surprised that some patients with pretty good vision—20/30 or 20/25—turn out to have a touch of hypotony maculopathy. So it's important to assess the condition of the macula. (Risk factors for hypotony maculopathy include young age, primary filtering surgery and myopia.)

I always recommend a macular OCT for postop patients with blurry vision. If I find hypotony maculopathy, I do the same thing as if I find corneal folds: I make sure the patient isn't using any glaucoma drops, and I look at the bleb to make sure it's not overfiltering or leaking.

Sometimes, there's not much you can do in this situation. If the posterior pole is involved and vision is affected, you can surgically close the trabeculectomy or tube. How-



If a patient complains of blurry vision postop it's a good idea to get a macular OCT, as hypotony maculopathy may be causing macular striae. If found, make sure the patient isn't still using preop glaucoma drops, and check the bleb for overfiltering and/or leaking. Top: Macular striae has caused vision to drop to 20/80. Bottom: Vision in this eye is 20/200.

ever, if the patient is still 20/20, you may just want to watch and wait. (Usually, if a patient is 20/20, most surgeons won't choose to go in for another surgery.)

Inflammation

Hypotony and inflammation are often intertwined, and ironically, either one can trigger the other. For example, mild inflammation—which can happen after almost any surgery—can cause the inflamed tissue to shut down its activity until the inflammation resolves. Intraocular inflammation often affects the ciliary body, and that can lead to decreased aqueous production and hypotony, resulting in blurriness and pain.

However, the reverse is also true: hypotony can lead to inflammation. A patient might have hypotony as a result of a valveless tube implant opening; all of a sudden, the pressure decreases. The eye notices the change and for reasons we don't entirely understand, it becomes inflamed. This can lead to macular edema, cell and flare in the anterior chamber, and ultimately a change in vision.

In most cases these issues will resolve on their own, but if they don't, my treatment would be to increase the topical steroids and start topical NSAIDs.

Getting Back on Track

As valuable as glaucoma surgery is, it can lead to postop issues, including refractive changes, astigmatism, induced myopia and variable vision. If your patient has low IOP and variability in vision, you need to determine the cause. Check for corneal folds and bleb leaks, and look at the macula; usually one of these will have an answer for you. Also, keep in mind that although we usually avoid surgery when the in-clinic vision measurement is close to 20/20, some causes of variable vision—such as bleb leaks or overfiltration—may require further surgical intervention. ◀

1. Gupta N. Incision-free minimally invasive conjunctival surgery (MICS) for late-onset bleb leaks after trabeculectomy (an American ophthalmological society thesis). Am J Ophthalmol 2019;207:333-342.

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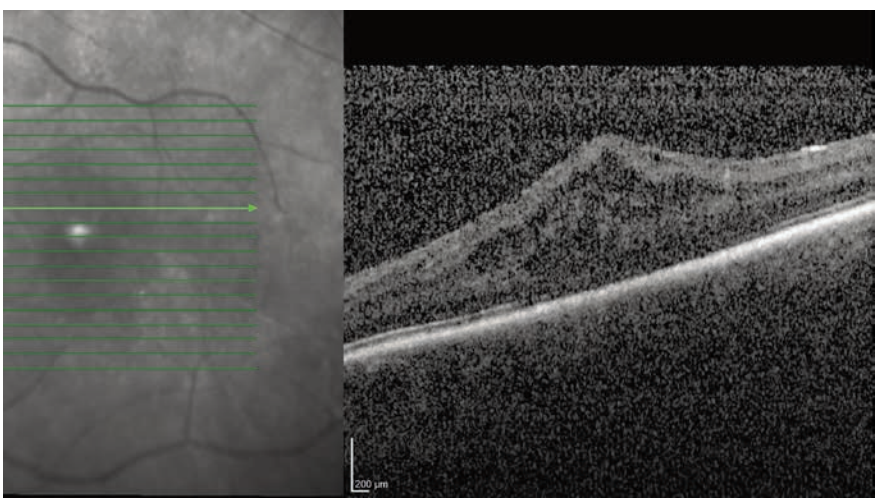

Inflammation can lead to hypotony (and vice versa). Inflammation inside the eye can cause ciliary body shutdown and decreased aqueous production, resulting in very low pressure.

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Surgical Pearls for PVR Procedures

Surgeons share expert tips on classifying, preventing and managing PVR in retinal detachment cases.

OLLYA FROMAL, MD, AND SONIA MEHTA, MD
PHILADELPHIA

Proliferative vitreoretinopathy is an aberrant vitreoretinal wound-healing process that leads to formation of proliferative contractile membranes following primary rhegmatogenous retinal detachment. PVR has been reported to occur in approximately 10 percent of RRD cases, with a higher incidence in cases with risk factors, and is the leading cause of RRD surgery failure.[1,2] PVR often leads to recurrent retinal detachments that are complicated in nature with a tractional component, require additional surgery, and have a guarded visual prognosis. Here, we'll provide advice on the best way to manage these cases surgically.

Pathophysiology

Understanding the development of PVR is helpful in preventing and managing it. Inflammation is an important initial step in PVR. Retinal detachment leads to ischemia and cell death, which results in breakdown of the blood-retinal barrier. This allows for an influx of cytokines, growth factors, blood-borne immune cells and other blood components.[3] Cytokines induce migration and proliferation of the resident retinal pigment epithelial cells, a major cell type involved in the pathogenesis of PVR. The RPE cells adhere to the retina, undergo transformation into mesenchymal cells and form proliferative fibrocellular membranes which acquire contractile abilities that can lead to complex rhegmatogenous and tractional retinal detachments.[4,5]

Risk Factors

Nearly all risk factors for PVR formation are related to liberation of retinal pigment epithelial cells and breakdown of the blood-retinal barrier.[6-8] Risk factors for postoperative PVR are related to the number and size of retinal breaks, extent of the retinal detachment and the presence of inflammation or PVR preoperatively.[9,10] Other identified risk factors include trauma—especially penetrating or perforating—giant retinal tears, prolonged inflammation of the posterior segment, viral infections of the posterior segment, prolonged chorioretinitis, vitreous hemorrhage and multiple previous surgeries. Additional risk factors include RDs with choroidal detachments and RDs associated with genetic syndromes. The incidence of postoperative PVR is higher in children and pediatric PVR is usually characterized by an aggressive course.[11]

Prevention

Presently there is no pharmacologic treatment proven to prevent PVR formation in its entirety. Current strategies for PVR prevention are focused on timely and successful repair of RRD. Care should be taken to avoid iatrogenic breaks in eyes with inflammation, endophthalmitis, chorioretinitis, and in pediatric RD, where the risk of PVR is increased.

Postoperatively, consider closely following patients who are at increased risk. The highest-risk period for PVR formation is four to 12

TABLE 1. RETINA SOCIETY UPDATED CLASSIFICATION OF PVR (1991)[13]

GRADE	CHARACTERISTICS
A	Vitreous haze, vitreous pigment clumps, pigment clusters on inferior retina
B	Wrinkling of the inner retinal surface, retinal stiffness, vessel tortuosity, rolled and irregular edge of retinal break, decreased mobility of vitreous
CP 1-12	Posterior to equator, focal, diffuse, or circumferential full-thickness folds, subretinal strands
CA 1-12	Anterior to equator, focal, diffuse, or circumferential full-thickness folds, subretinal strands, anterior displacement, condensed vitreous strands

This article has no commercial sponsorship.

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

weeks following primary RD repair.

Features and Classification

Clinically, early stages of PVR are characterized by cellular dispersion in the vitreous and white opacification of the retinal surface with increased reflectance and a cellophane-like appearance. Retinal tears can have rolled edges, retinal folds can have fine membranes between them, and the mobility of the detached retina is reduced. The hallmark feature of PVR is formation of preretinal membranes, resulting in retinal wrinkling and characteristic fixed star-fold formation. In severe cases of PVR, narrow or closed funnel detachments form.

The most popular classification scheme remains that which was published by the Retina Society Terminology Committee in 1983. In this classification, PVR is subdivided into four stages of increasing severity, A to D, that run from minimal to massive.[12] (Some limitations of this classification have been identified, including lack of specified location and magnitude of traction.) In 1991, the updated Retina Society Classification eliminated grade D PVR and expanded on grade C, emphasizing the posterior vs. anterior locations of proliferation, added various types of contraction and added the ability to note the extent of the disease in clock hours *(See Table 1 on p.78)*.[13] This new classification is detailed and, while it's somewhat difficult to incorporate into clinical practice, it provides standardized nomenclature that's useful for clinical trials.[14] Even so, PVR classification is a useful tool for grading severity, discussing patient expectations, communicating with colleagues and performing research.

PVR is a clinical diagnosis. Occasionally, in cases of media opacity limiting a view to the fundus, ancillary imaging, such as ultrasonography, is necessary. Dynamic ultrasonography is especially helpful in this scenario and reveals less retinal mobility during the exam in patients with PVR-related RD, due to fixed retinal folds.

Management

Given the lack of effective medical therapy, surgery is the main treatment for PVR. Timing of PVR surgery depends on the case. Some authors advocate delaying surgery in early cases of postoperative PVR out of a concern for heightening the inflammatory response and stimulating further PVR formation if additional procedures are performed.[15-17] Furthermore, delaying repair leads to the formation of mature membranes, which are generally easier to remove than fragile, immature membranes that are difficult to remove in sheets.[17] In cases that are vision-threatening, however, early intervention is recommended.

PVR-related RD repair is a complex vitreoretinal procedure with multiple factors at play, and careful planning is key to successful retinal reattachment and prevention of further proliferation. Lens status is an important factor to

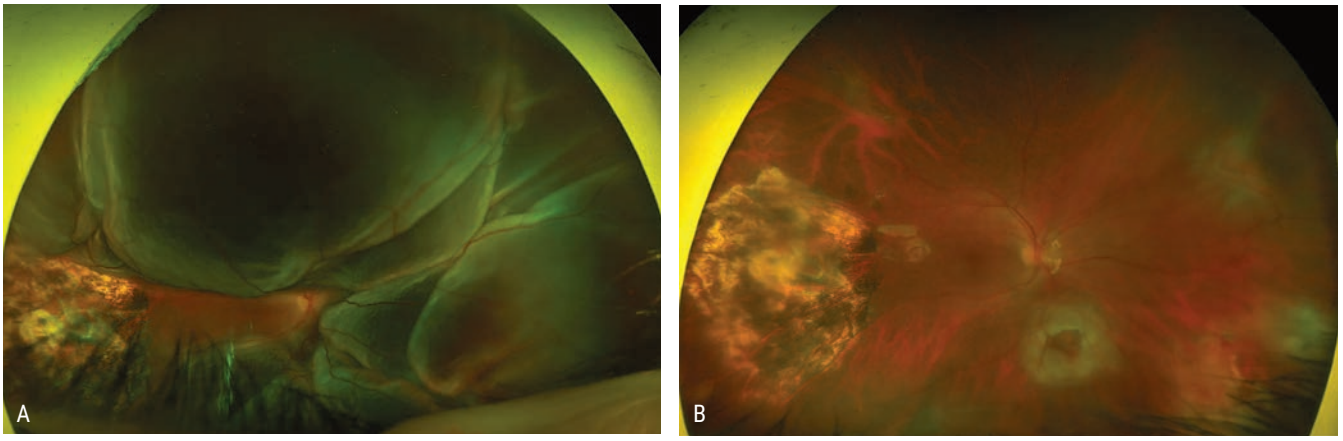

Figure 1. A) Preoperative fundus image of a 44-year-old man referred for proliferative vitreoretinopathy following vitrectomy for a posterior intraocular foreign body with an impact site temporal to the macula. The patient has a near total retinal detachment with multiple posterior and peripheral starfolds. B) Postoperative fundus image showing a successfully attached retina following vitrectomy and membrane peeling, retinotomy, drainage of subretinal fluid, endolaser and silicone oil. The preretinal membranes were peeled and the ILM was peeled over the macula to the periphery using ICG for visualization of the ILM.

consider prior to surgery. In patients with visually significant cataracts or cataracts that will likely mature during the postoperative period and affect visualization of the posterior segment, consider cataract surgery with IOL placement. In patients with anterior PVR, surgeons should also consider lensectomy with capsule removal to allow for complete removal of anterior pathology. Another factor to consider preoperatively is placement of a scleral buckle. If a buckle wasn't placed at the time of the previous surgery, consider placing one at the time of reoperation if you don't plan on doing an extensive relaxing retinectomy.

In patients with complex RDs, it's important to have a thorough discussion with the patient and key family members regarding the surgery and prognosis. Afterwards, give them plenty of time to ask questions, and address these questions. In patients in whom we're planning to use silicone oil, we emphasize the multi-step nature of the process.

Intraocular preservative-free triamcinolone acetonide, such as Triesence (Alcon) can be used to highlight the vitreous, ensuring adequate removal of the posterior hyaloid and vitreous base. If cortical vitreous is present, it can be removed with a diamond-dusted membrane scraper (Synergetics) or a flexible nitinol loop (Alcon). Next, we meticulously remove all preretinal membranes. We may also peel the ILM, which can serve as a scaffold for PVR proliferation and potentially decreases recurrence of posterior ERM formation and recurrent detachment.[18-20] We use indocyanine green or brilliant blue dye (TissueBlue, Dutch Ophthalmic USA) to stain the ILM, and peel posteriorly and as far out to the periphery as possible *(Figure 1)*.

Subretinal PVR membranes—if isolated, extrafoveal and not exerting tractional forces—may not need to be removed for retinal reattachment. However, in cases requiring removal, we like to use chandelier illumination, placement of an extramacular retinotomy, and forceps in a hand-to-hand technique to remove the membrane.

After peeling, if the retina still appears stiff and unable to flatten, a relaxing retinectomy—a circumferential excision of retinal tissue—may be necessary to relieve traction. We try to perform the retinectomy as far anterior as possible, to preserve functional retina. It's also important to incorporate any potentially problematic retina into the retinectomy, if not too posterior. We like the edge of the retinectomy to be healthy and free of PVR membranes, contracture and traction. We use diathermy to create a continuous line to delineate where we want to create the incision. Diathermy is also helpful for hemostasis. Careful steps should be taken to minimize bleeding during the retinectomy, as hemorrhage will carry blood-derived cytokines which can promote recurrent PVR. In very severe cases, a 360-degree retinectomy may be necessary to achieve retinal flattening.

Following a retinectomy, we use perfluorocarbon liquid (PFCL) to flatten the retina. When instilling the PFCL, tilt the eye away from the retinectomy to ensure the subretinal fluid is maximally squeezed out, and also to help prevent folding of the retinectomy edge. Then do a careful air-fluid exchange, starting anteriorly in the fluid phase and then draining the subretinal fluid starting at the anterior edge of the retinectomy and moving more posteriorly as the exchange progresses. Also, rotate the eye in the direction of the retinectomy to remove as much subretinal fluid as possible. At the end, place a few drops of balanced saline solution posteriorly to aspirate any residual PFCL.

Excessive laser is unnecessary and can be proinflammatory. We typically place two rows of laser at the posterior edges of the retinectomy and reinforce the anterior points of

the retinectomy at 3- and 9-o'clock with some additional laser using an illuminated endolaser and scleral depression.

In eyes with extensive PVR or large retinectomies, silicone oil tamponade is recommended. In eyes that are aphakic or where pupillary block is a concern, it's important to place an inferior iridotomy when using silicone oil. Having the patient position face down postoperatively can be helpful in preventing development of folds.

Close follow-up and careful postoperative management following PVR surgery are essential for success and good visual outcomes. It's important to watch for and treat intraocular inflammation, cystoid macular edema and hypotony. Patients may also develop epiretinal membranes or tractional macular edema which, if visually significant, can be treated to help enhance visual outcomes. Silicone oil-related issues include emulsification leading to ocular hypertension or band keratopathy. Early recognition and treatment of these complications is vital to maintaining the success of the PVR surgery and improving visual outcomes.

Future Directions

Several pharmaceutical agents have been employed over the years in attempts to reduce the rate of postoperative PVR recurrence, with variable success. Considering inflammatory mechanisms of PVR formation, corticosteroids present as a logical treatment of choice. However, studies have failed to show a difference in final visual acuity between treatment (systemic or intravitreal steroids) and control groups.[21-23] Antineoplastic drugs, such as 5-fluorouracil and daunorubicin, displayed mixed results. In addition, their use is limited by systemic toxicity.

A promising agent in the treatment of severe postoperative PVR is the antimetabolite agent methotrexate. Weekly intravitreal methotrexate injections of 400 mcg/0.05 mL beginning intraoperatively have been successfully employed to reduce PVR-associated recurrent detachment in high-risk patients.[24,25] Currently, a prospective, randomized clinical trial is under way that aims to assess the efficacy of postoperative intravitreal methotrexate in prevention of PVR-associated redetachment.[26]

In conclusion, modern advances in vitreoretinal surgery allow for successful retinal reattachment in most cases of PVR. However, despite anatomic success, visual outcomes are variable. Timely diagnosis, a thoughtful surgical approach and careful postoperative management are key to successful retinal reattachment and vision preservation. ◀

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Dr. Mehta practices at Mid-Atlantic Retina, the Retina Service of Wills Eye Hospital; and is an assistant professor at Thomas Jefferson University Hospital.

Central VF Loss in Disc-Hemorrhage Patients

Researchers assessed the characteristics and rate of central visual field loss after optic disc hemorrhages, as part of a prospective cohort study.

A total of 343 eyes of 220 subjects who had at least three years of follow-up with a minimum of five visits with 10-2 and 24-2 visual fields were recruited. Rates of 10-2 mean deviation (MD) loss in each hemifield and pre-defined zones were compared using a linear mixed-effects model in DH and non-DH eyes. Clustered pointwise regression analysis defined central VF progressors, and researchers compared findings to 24-2 VF loss using Guided Progression Analysis.

A total of 39 eyes with DHs and 304 eyes without DHs had a mean follow-up of 5.2 years. Here are some of the findings:

• Eyes with DHs had rates of 10-2 mean deviation (MD) loss that were three times faster than non-DH eyes (mean difference [CI] -0.36 dB/year [0.54, 0.18; p<0.001) and were 3.7 times more likely to progress (p=0.002).

• A larger proportion of glaucomatous eyes showed central VF progression rather than peripheral VF progression (30.8 percent vs. 20.5 percent) in the DH group, compared with the non-DH group (10.9 percent vs. 9.2 percent).

• In early glaucoma, the rate of 10-2 MD loss was 5.5 times faster in DH eyes than in non-DH eyes (p<0.001).

• Superonasal and superotemporal central VF regions progressed more rapidly than other regions, especially in DH eyes.

Researchers found that central visual field loss was accelerated in glaucoma eyes with optic disc hemorrhages and corresponded topographically to the DH location. They suggest that for glaucoma patients with DHs, clinicians should consider supplementing 10-2 VFs with 24-2 VFS to monitor disease.

Am J Ophthalmol 2021; June 6 [Epub ahead of print].
David RCC, Moghimi S, Do JL, et al.

Dry-eye Subtypes Explored

Scientists evaluated subtypes and characteristics of dry eye using conventional tests and dynamic tear interferometry, and reported determinants of disease severity in each DE subtype.

A total of 309 patients were diagnosed with DE, and 69 healthy controls were prospectively enrolled. All eyes were evaluated using the Ocular Surface Disease Index (OSDI), Schirmer's test I (ST1) and meibomian gland dysfunction (MGD) grade. The tear interferometric pattern and lipid layer thickness were determined using DR-1α and LipiView II, respectively.

Here are some of the findings:

• Dynamic interferometric analysis revealed 56.6 percent of patients with DE exhibited Jupiter patterns, indicative of aqueous-deficiency, while 43.4 percent exhibited crystal patterns, indicative of lipid deficiency. These findings were in accordance with classification based on ST1 scores and MGD grade.

• Conventional assessment indicated 286 patients exhibited evidence of evaporative DE (EDE) due to MGD, while 11 exhibited signs of pure aqueous-deficient DE (pure ADDE, only ST1 ≤5 mm).

• Of 286 patients with EDE, 144 were categorized into the mixed-ADDE/EDE group, in which ST1 was identified as a strong negative determinant of OSDI.

• In contrast, 72.2 percent of patients with mixed-ADDE/EDE exhibited Jupiter patterns (Jupiter mixed), while 27.8 percent exhibited crystal patterns (crystal mixed).

• OSDI values were significantly higher in the crystal-mixed group than in the Jupiter-mixed, where OSDI scores were independently associated with ST1 values only.

Scientists reported that the majority of EDE patients also exhibited aqueous deficiency, which can aggravate symptoms in patients with lipid-deficient mixed-ADDE/EDE. They recommended that conventional assessments be combined with interferometric tear analysis to determine the most appropriate treatment for each DE patient.

Br J Ophthalmol 2021; June 9 [Epub ahead of print].
Ji YW, Seong H, Seo JG, et al.

PDR Progression in the Real World vs. Trials

While clinical trials have demonstrated that treatment of diabetic macular edema with anti-VEGF drugs can ameliorate disease severity and progression, little evidence has shown if these outcomes translate to real-word settings.

To get answers, researchers in the United Kingdom analyzed what they said is the largest cohort of DME patients who received anti-VEGF treatments and were evaluated

for development of proliferative diabetic retinopathy in a real-world setting. They recently presented their results at the Association for Research in Vision and Ophthalmology.

Baseline DR grade is an important influential factor for PDR development during DME treatment, the researchers noted. They add that DR improvement in clinical trials may not be reproduced in routine-care settings where patients receive fewer treatments and could have less rigorous diabetes mellitus control.

The study analyzed data on 4,922 patients from 27 centers in the United Kingdom. The patients received anti-VEGF injections for DME between February 2013 and December 2018, and the centers used the same electronic medical record system. The median patient age (standard deviation) was 66.4 years (11.9 years) and median follow-up was 13 months (15.29 months). Fifty-eight percent of the patients were men.

The primary outcome was the time from the first DME treatment to progression to PDR. The study used time-to-event analysis to demonstrate the rate of PDR progression stratified by baseline DR grade.

On average, the patients received 6.3 (SD 6.3) treatments during the study period. Patients with more severe DR grades required more injections: 5.81 injections for mild nonproliferative DR, 6.56 for moderate NPDR and 6.84 for severe NPDR.

Progression to PDR was strongly influenced by baseline DR grade. But when the researchers controlled for baseline DR grade, a higher number of injections, using six as a threshold between lower and higher number, didn't reduce the risk of PDR development.

"This will help inform clinicians about the importance of carefully following these patients and adjusting their follow-up intervals accordingly as these injections may not change the disease course in the long term," Dr. Alsaedi said.

Dr. Alsaedi and co-authors have no disclosures.

Paper presented at Association for Research in Vision and Ophthalmology. Diabetic Retinopathy – Diagnosis and Therapies session; May 6, 2021.
Alsaedi AH, Herren T, Thomas D, et al.

Silver Nanoparticles Reduce Acanthamoeba Risk

Acanthamoeba keratitis is particularly common among contact lens wearers, occurring most often due to improper storage or failure to remove the lenses prior to showering or swimming. Recently, a study evaluated silver nanoparticles as possible agents against *Acanthamoeba* and found that low concentrations in contact lens solution might help to decrease infection risk.

The researchers examined properties of silver nanoparticles (AgNPs) when conjugated with five multipurpose contact lens solutions against the NEFF strain of *Acanthamoeba* in five *in vitro* assays. Here are some of their findings:

- Opti-Free (Alcon) reduced *Acanthamoeba* activity by up to 27.8 percent after three hours and 23.8 percent after four hours of incubation, compared to a pure contact lens solution. The researchers noted that they observed increased activity after up to six hours of incubation, which is the minimum time of disinfection for Opti-Free.
- SoloCare Aqua (Menicon) demonstrated reduced activity up to 17.2 percent after three hours and 20.3 percent after four hours of incubation compared to a pure contact lens solution.
- B-Lens, Best View and ReNu MultiPlus (Bausch + Lomb) demonstrated no statistically significant increase in anti-amoebic activity after up to six hours of incubation when conjugated with the silver nanoparticles.

When conjugated with silver

Big Data

(Continued from p. 73)

those data points," she notes. "But that's farther in the future. In the meantime, our trajectory is to try to incorporate clinical images, because they're used so much in diagnosis and treatment. They give us a more complete picture of patients and their disease status and severity. That's what we're working toward."

Dr. Williams says Vestrum Health is working on incorporating practice management and billing data into the system, and then correlating that with data from the EHR. "We have the ability to provide practices with billing data statistics and compare it to their peers around the country, as well," he explains. "We're working with companies that have claims databases, to merge our granular and nuanced EHR data with that information. That will allow us to do an even more sophisticated analysis of the delivery of health care in retina."

Dr. Williams believes the future of big data is very promising. "Ideally, you need to have a well-organized, representative database that includes all of the EHR data fields—including the text fields—that contain useful data," he says. "And you have to have good people, and possibly AI, to analyze the data. But I think in the long run, big data in health care is going to have tremendous value. It's a matter of us identifying and accessing that value."

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nanoparticles, The Opti-Free and SoloCare Aqua contact lens solutions demonstrated a significant increase in anti-amoebic activity without increasing overall cytotoxicity, researchers said.

Pathogens 2021;10:5:583.
Hendiger EG, Padzik M, Sifaoui I, et al.

Ocular Allergy's Impact Surprisingly Severe in Kids

The severity of allergic conjunctivitis may cause children with the condition—and their parents—to have a lower quality of life, a recent study published in *JAMA Ophthalmology* suggests.

The condition is especially problematic in children and adolescents, the study notes.

The case-control study enrolled 188 children and their parents. Participants included 92 children between the ages of 5 and 18 and their parents in the study group, and 96 healthy, age-matched youths and their caretakers in the control group.

The members of the study group were subdivided into cohorts of vernal keratoconjunctivitis, atopic keratoconjunctivitis, seasonal allergic conjunctivitis and perennial allergic conjunctivitis.

Participants responded to the Pediatric Quality of Life Inventory Questionnaire (PedsQL), with scores ranging from zero to 100. Higher scores on the questionnaire indicated better health-related quality of life and fewer negative findings.

Key findings from the study include:

- PedsQL scores were 27 points lower in children with allergic conjunctivitis and their parents compared with their counterparts in the control group.
- Having vernal keratoconjunctivitis or atopic keratoconjunctivitis reduced QOL by about another four points than the mean for all allergy subjects.
- In the allergic conjunctivitis group, a higher corneal fluorescein staining score was linked with a lower quality of life in children.
- Parents whose children had higher corneal fluorescein staining scores and multiple clinical consultations reported a lower quality of life. Considering sub-scores, parents were most worried about whether their child's treatment would be effective.
- Parents' scores correlated with their children's.

The decreased quality of life in children with allergic conjunctivitis was actually worse than in previous studies of youth diagnosed with blinding diseases such as glaucoma and congenital cataract.

The study's results suggest a detailed assessment of quality of life may be useful to inform chronic condition care for children with allergic conjunctivitis, the investigators concluded. ◀

JAMA Ophthalmology 2021; June 10 [Epub ahead of print].
Zhang SY, Li J, Liu R, et al.

Maximizing SMILE Outcomes

(Continued from p. 22)

of 20/20 or better in 89 percent of post-SMILE patients,[15] significantly fewer HOAs,[1] good patient satisfaction,[14,16] higher biomechanical stability of the postop cornea,[14,16] fewer inflammatory cells in the cornea,[9] less severe denervation and accelerated neuronal healing.[7] Numerous meta-analyses have demonstrated that the long-term efficacy, predictability and safety outcomes of SMILE are comparable to those of femtosecond-LASIK.[7,15]

Because SMILE is a relatively new procedure, we need to await the results of additional clinical trials to validate these perceived advantages. Nonetheless, as I hope I've demonstrated, SMILE is a procedure that's worth learning and one that won't produce unacceptable complications if you proceed carefully, especially as you begin to climb that initial learning curve. ◀

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DISCLOSURES:

Dr. Moshifar is the director of clinical research at the Hoopes Vision Research Center in Draper, Utah, adjunct professor at the Moran Eye Center and co-director of the Utah Lions Eye Bank. He has no financial interest in the products mentioned.

(Continued from p. 64)

them into two groups: diabetic retinopathy and sickle cell retinopathy, with 95.01 percent sensitivity and 92.25 percent specificity.

After sorting into corresponding retinopathies, the support vector machine conducted the condition staging classification: It had 92.18 percent sensitivity and 86.43 percent specificity for nonproliferative diabetic retinopathy staging (mild vs. moderate vs. severe), and 93.19 percent sensitivity and 91.60 percent specificity for sickle cell retinopathy staging (mild vs. severe).

The Future

Dr. Boyer believes that the use of OCTA will continue to increase. "OCTA allows us to see layers of the retina that we couldn't see," he says. "In other words, there are evidently three capillary plexuses, and we can only see one on fluorescein angiography. Now, we're seeing two. We can see a superficial and a deeper area of capillary circulation and that's giving us a better idea of where ischemia is occurring. So, I think OCTA is adding to our knowledge of different disease states because we're now able to visualize areas we couldn't visualize before."

Dr. Lim agrees. "In the future, I'd like to think that every retinal specialist would have one in his or her office, if the cost came down enough so that it was affordable. Second, if the noise-to-signal ratio can be improved, I think it probably will become more mainstream," she says.

She explains that manufacturers are currently working to improve the software. "If you remember, when first-generation optical coherence tomography first came out, people said they would never use it," she says. "Some pretty famous retina specialists said OCT would never catch on. They said they would never use it because the images were too fuzzy, so you couldn't tell what's real and what wasn't. Then, with the later-generation OCT units, with improved image quality, OCT caught on like wildfire. Now, essentially every retinal specialist has an OCT. I think the same thing will happen with OCTA." ◀

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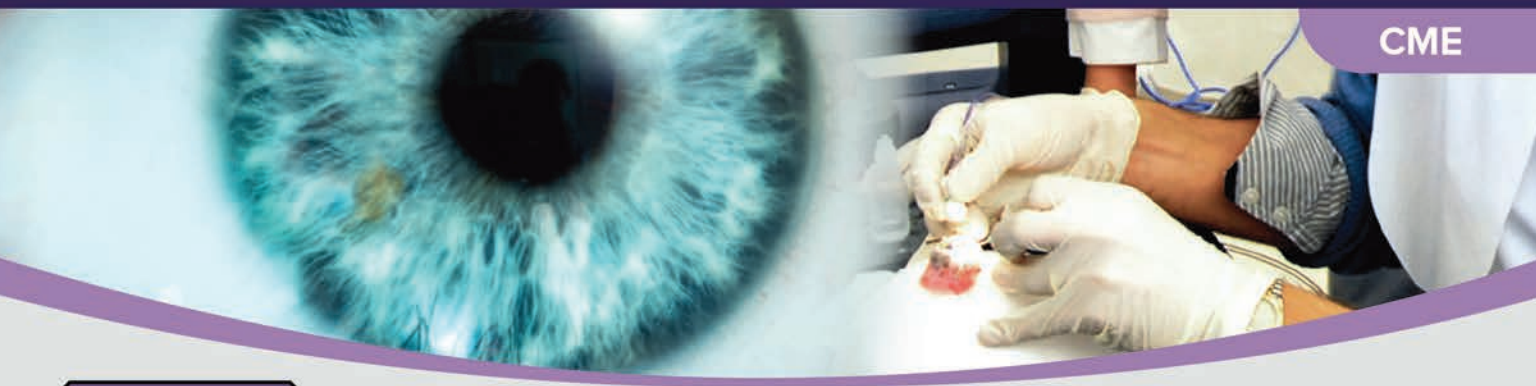

CME

CSE 3RD YEAR RESIDENTS CONTINUING SPECIALIZED EDUCATION

3RD YEAR RESIDENT PROGRAMS & WET LAB

Dear CSE 3rd-Year Resident Program Director and Coordinator,

We would like to invite you to review the upcoming 3rd-Year Ophthalmology Resident Programs and Wet Labs for 2021. The programs offer a unique educational opportunity for third-year residents by providing the chance to meet and exchange ideas with some of the most respected thought leaders in ophthalmology. The programs are designed to provide your residents with a state-of-the-art didactic and wet lab experience. The programs also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your residents to attend one of these educational activities, which are CME accredited to ensure fair balance. Residents will select one of three dates for the live, **virtual** didactic program and one of three dates for the in-person, hands-on wet lab in Fort Worth.

Best regards,
Course Directors

THIRD-YEAR RESIDENT **LIVE**, VIRTUAL DIDACTIC PROGRAMS

JULY 31, 2021	AUGUST 7, 2021	AUGUST 14, 2021
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A young woman presents with what appears to be atypical, unilateral uveitis.

LUCY COBBS, MD, RALPH C. EAGLE JR, MD, ANTONIO YAGHY, MD, AND CAROL L. SHIELDS, MD PHILADELPHIA
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Presentation

A 27-year-old female was referred to a local ophthalmologist with recurrent unilateral uveitis of her left eye. She had a one-year history of recurrent episodes of transient vision loss OS. Evaluation revealed elevated intraocular pressure of 56 mmHg and anterior chamber inflammation OS, for which she was treated with brimonidine twice a day, dorzolamide-timolol twice a day, netarsudil-latanoprost at bedtime nightly, acetazolamide 500 mg twice a day by mouth, and prednisolone acetate eye drops four times a day. She was also started on oral valacyclovir 1 gram three times daily due to concern for a herpetic infection.

At one-month follow-up, there was persistent anterior chamber inflammation with granulomatous keratic precipitates and a fixed pupil OS. Difluprednate was substituted, and she underwent an anterior chamber paracentesis, which was negative for varicella zoster virus, herpes simplex virus and cytomegalovirus. At six-months follow-up, IOP OS remained above 30 mmHg despite maximal medical therapy, so an Ahmed tube shunt was placed superotemporally. However, IOP remained elevated in the range of 30 to 50 mmHg, which was attributed to corticosteroid response, so topical corticosteroids were discontinued. Intraocular inflammation worsened, so difluprednate twice a day was restarted, and acyclovir was switched to ganciclovir four times a day.

The patient was referred to a uveitis specialist, who diagnosed intraocular malignancy, based on clinical examination and ultrasound biomicroscopic findings, and the patient was referred to the Ocular Oncology Service at the Wills Eye Hospital for biopsy and management.

An extensive uveitis workup prior to presentation was negative for tuberculosis, syphilis, angiotensin-converting enzyme, lysozyme and HLA-B27. A chest computerized tomography scan showed calcified and noncalcified granulomas in the left lower lobe and densely calcified mediastinal and hilar nodes, which were interpreted as possible sequelae of prior histoplasmosis infection.

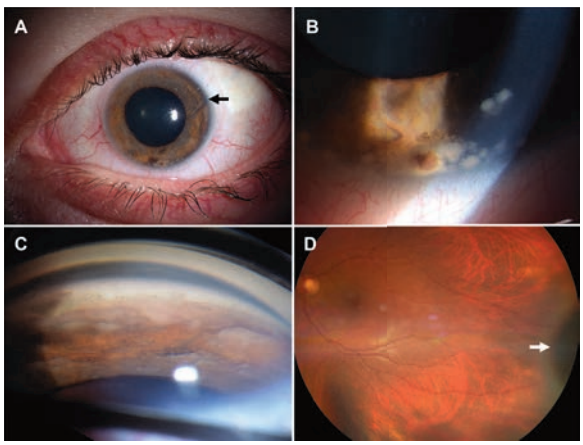

Figure 1. External findings in a 27-year-old female. (A) Conjunctival injection and an Ahmed tube shunt superotemporally (black arrow) are noted, as well as (B) deposits with gray-white debris and a 5-percent hypopyon of cellular aggregates inferiorly. (C) Gonioscopy reveals white deposits coating the inferior iridocorneal angle. (D) Funduscopically, the left eye appeared normal but there was a temporal dark shadow (white arrow), suspicious for mass.

Medical History

The patient's past medical history revealed hypothyroidism and migraine headaches without ocular involvement. Family history was remarkable for multiple sclerosis in her maternal aunt, breast cancer in her maternal grandmother and lung cancer in her maternal grandfather.

Exam

On examination, the patient's best-corrected visual acuity was

20/20 OD and 20/40 OS. The pupils were 3 mm OD and 7 mm OS in the dark, with minimal reactivity to light and a relative afferent pupillary defect OS. The IOP was 17 mmHg OD, and 31 mmHg OS. Confrontation visual fields and extraocular movements were full. Slit lamp biomicroscopy OS revealed the Ahmed valve in place superotemporally *(Figure 1A, arrow)*, gray-white deposits coating the corneal endothelium, iris stroma and angle *(Figure 1B);* and a 5-percent hypopyon composed of clumps of focally pigmented cells inferiorly *(Figure 1C)*. Aggregates of cells also were noted in the lumen of the Ahmed tube shunt *(Figure 1A, arrow)*. Gonioscopy revealed focal anterior synechiae and gray-white deposits blanketing the inferior angle and iris *(Figure 1C)*. Dilated fundus examination disclosed a flat retina and intact macula, no vitreous cells and a normal optic disc. A dark shadow, suspicious for a mass, was noted in the far temporal periphery in the ciliary body *(Figure 1D, white arrow)*. Examination of the right eye was unremarkable with no inflammation or tumor.

What is your diagnosis? What further workup would you pursue? The diagnosis appears below.

Work-up, Diagnosis and Treatment

The clinical picture wasn't consistent with infectious or non-infectious uveitis; instead, the clumps of cells coating the anterior chamber were only consistent with a malignancy. B-scan ultrasonography showed a flat retina without choroidal mass or retinal detachment. Anterior segment optical coherence tomography showed thickening of the iris with deposits surrounding the tube shunt *(Figure 2A, white arrows)*. Ultrasound biomicroscopy disclosed a 3-mm thick, dome-shaped echolucent mass in the ciliary body stroma extending from 12 o'clock to 4 o'clock with no extrascleral extension *(Figure 2B)*. The mass measured 20 mm in length and involved only the ciliary body.

The differential diagnosis for the ciliary body mass included neoplasms of the ciliary body stroma, most likely malignant melanoma. Other rarer entities included schwannoma, leiomyoma, lymphoma, metastasis and inflammatory disorders such as juvenile xanthogranuloma and Langerhans histiocytosis. Fine needle aspiration biopsy of the anterior chamber debris and ciliary body mass disclosed discohesive epithelioid cells with scant pigment and high nuclear-cytoplasmic ratio and prominent nucleoli, suspicious for melanoma. The cells were immunoreactive for melanocytic markers Melan-A and HMB 45. The cells also co-expressed cytokeratin marker AE1/AE3, but the intrastromal location of the tumor excluded a ciliary body epithelial tumor. Uveal melanoma seemed most likely, based on the tumor's clinical, cytopathologic and immunohistochemical features.

Management options included plaque radiotherapy or enucleation. Plaque radiotherapy wasn't a reasonable option due to the extensive tumor size with total aqueous seeding and the presence of a tube shunt with possible extraocular tumor seeding, so the left eye was managed with enucleation. Intraoperatively, care was taken to avoid violating the capsule of the tube shunt and prevention of tumor seeding, so the globe and tube shunt were removed together as one piece. Gross pathology showed

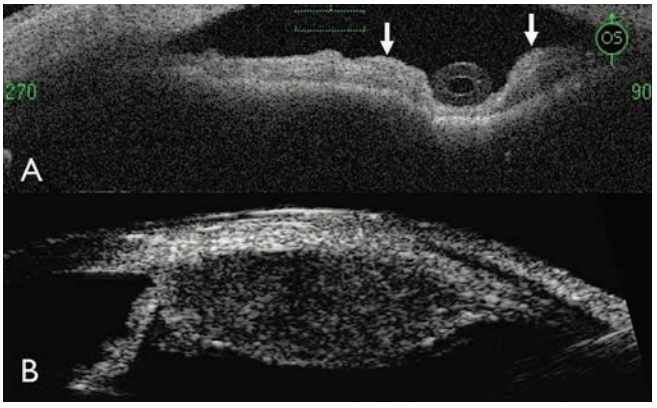

Figure 2. (A) Anterior segment optical coherence tomography shows thickening of the iris with surface deposits (white arrows) surrounding the tube shunt. (B) Ultrasound biomicroscopy discloses a 3-mm thick, dome-shaped echolucent mass in the left ciliary body.

a ciliary body mass that measured 20 mm in circumferential base, 8 mm in anteroposterior base and 2.5 mm in thickness *(Figure 3A)*.

Histopathology disclosed epithelioid-cell-rich mixed-cell melanoma with mitotically active "hotspots" containing two to three mitoses per high-power field *(Figure 3B)*. The tumor cells were mitotically active, and their nuclei failed to stain for BRCA1-associated protein 1 (BAP1), consistent with a BAP1 mutation and a significant risk for metastatic disease *(Figure 3C)*. The tumor involved the peripheral iris and had spawned a population of discohesive amelanotic epithelioid cells that seeded the anterior segment, blanketing the iris and angle and forming the deposits and clumps of cells that were initially misinterpreted clinically as granulomatous inflammation *(Figure 3D, black arrows, Figure 3E)*.

Clinical examination of the tube shunt revealed tumor cells within the shunt *(Figure 4A)*, and that the globe with the shunt capsule (white arrow) was intact following enucleation *(Figure 4B)*. The fluid contents of the shunt disclosed melanoma cells that had extended into the drain-

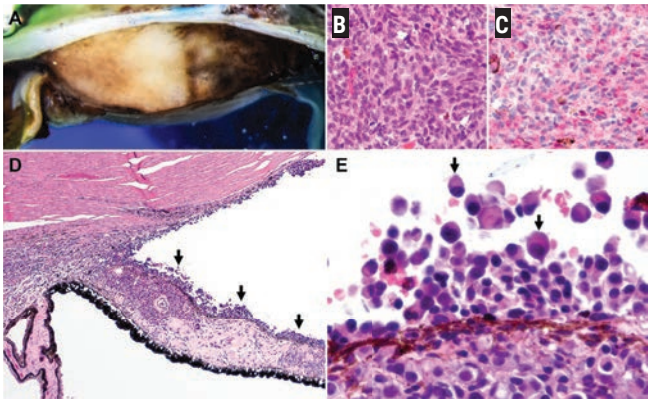

Figure 3. (A) The enucleated eye reveals a partially pigmented ciliary body mass measuring 8 mm anteroposteriorly and 3 mm in thickness. (B, C) Histopathology discloses an epithelioid-cell-rich, mixed-cell melanoma of the ciliary body with 44 mitotic figures counted in 40 high-power fields. (D, E) The tumor also involved parts of the iris and a population of tumor cells clumping on the anterior iris surface (black arrows), which had been misinterpreted clinically as granulomatous inflammation.

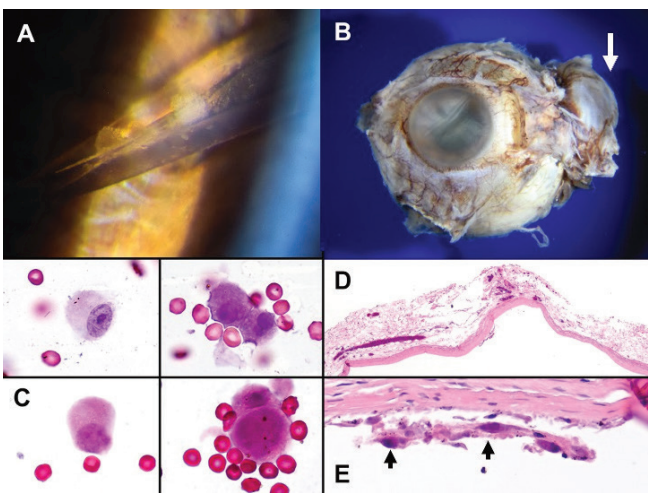

Figure 4. (A) The lumen of the superotemporal tube shunt contains deposits of white tumor tissue. (B) The eye was enucleated with the capsule of the tube shunt (white arrow) intact. (C) Fluid from the tube reservoir was aspirated, and cytologic examination disclosed melanoma cells. (D, E) Histopathology of the encapsulated epibulbar reservoir also showed tumor cells that had extended extraocularly (black arrows).

age device *(Figure 4C)*. The shunt capsule revealed rare tumor cells, some of which had extended extraocularly *(Figure 4D, Figure 4E, black arrows)*. Additional orbital biopsies were tumor-free. The final diagnosis was mitotically active ciliary body "ring" melanoma with tumor seeding into the anterior segment and extension into the Ahmed valve shunt.

The patient healed well, and a prosthesis was placed. She was referred to a melanoma oncologist for consideration of adjuvant Sunitinib, a receptor protein-tyrosine kinase inhibitor, to help prevent metastatic disease. The results of her tumor genetic testing showed chromosome 3 monosomy and multiple 8q amplifications consistent with The Cancer Genome Atlas (TCGA) Group D, implying a high risk for metastasis. Blood test for germline BAP1 mutation is pending. Going forward, she'll require regular surveillance with magnetic resonance imaging of the orbit, liver function tests, liver MRI and chest X-rays to monitor for metastatic disease.

Discussion

Ciliary body melanoma is rare, comprising 6 percent of all uveal melanomas, with uveal melanomas occurring at an incidence of 5.1 cases per million per year.[1] In addition, CB melanomas infrequently occur in people under the age

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of 30, as in this patient's case.[2] Diagnosis of CB melanoma is challenging, since the tumors are often hidden behind the iris without retinal detachment, until they become large and possibly sublux the lens.[2,3] Consequently, the tumors are often advanced by the time they're diagnosed, with a mean basal thickness of 6.6 mm at diagnosis.[1] Ultrasound is a useful tool for identifying ciliary body melanoma.[3,4]

It's not unprecedented for an intraocular tumor to cause increased intraocular pressure and glaucoma.[5] In a study of over 2,500 eyes with intraocular tumors, 5 percent were found to have secondary glaucoma.[6] It's estimated that 17 percent of CB melanomas result in secondary glaucoma.[6] This can occur by a variety of mechanisms, including direct tumor invasion of the iridocorneal angle, inflammation from tumor necrosis, pupillary block, tumor seeding into the angle and iris neovascularization.[5-8] One study analzyed five glaucomatous eyes that had undergone implantation of tube shunts and were subsequently found to have undiagnosed intraocular tumors: Two had medulloepithelioma and three had uveal melanoma.[5] The eyes were misdiagnosed with various types of glaucoma for a mean timespan of more than five years prior to the discovery of tumor on histopathology. Four of the five enucleated eyes had extrascleral tumor extension, and three had extraocular tumor cells in the tube shunt reservoirs.[5] The authors concluded that tube shunt implants can provide a pathway for extraocular tumor spread, and they speculated that the difficulty in visualizing a ciliary body tumor was a crucial factor in the failure to recognize tumor-induced glaucoma.[5]

Less commonly, ciliary body melanoma can masquerade as sclerouveitis, which is thought to be caused by tumor necrosis inducing inflammation, and the presence of sentinel episcleral vessels, simulating scleritis.[9,10] In one case series, two patients were misdiagnosed with scleritis from misinterpretation of sentinel episcleral vessels feeding the tumor and inflammation, which transiently improved with oral and topical corticosteroids.[11] Others have observed patients with uveitis, including anterior chamber inflammation, yellow nodules on the iris and injected eyes, who in fact had occult uveal melanoma.[9,10,11] In many of these cases, imaging was an important diagnostic tool for identifying tumors in eyes misdiagnosed as having chronic uveitis. In particular, UBM offers a fairly high-resolution tool for visualizing the ciliary body at all clock hours for detection of tumors that might not be seen on examination.

Our patient was unique not only in her presentation, but also in her young age (27). Testing for BAP1 syndrome is an important part of the workup for patients who are young or have a family history of multiple cancers, including melanoma.[12] BAP1 is a tumor-suppressor gene located on chromosome 3p21.1. When BAP1 is mutated, patients are predisposed to a variety of cancers including uveal melanoma, malignant mesothelioma, renal cell carcinoma, cutaneous melanomas and basal cell carcinoma.[2,12] In a prior review of approximately 500 patients with uveal melanoma, 5 percent had BAP1 polymorphisms, which were associated with larger tumors and an increased incidence of ciliary body involvement.[2,13]

In addition to testing for germline BAP1 mutations, assessing for somatic BAP1 mutation in the tumor helps to stratify the risk for tumor metastasis. Researchers found that somatic BAP1 mutation within the intraocular melanoma was significantly associated with an increased risk for systemic metastasis.[14,15] On histochemical immunostaining of this patient's tumor, there was evidence of BAP1 somatic mutation, suggesting substantial risk for metastatic disease. The molecular cascade involving BAP1 appears to be linked to tumor metastasis and may be a target for treatment in the future.[15] ◀

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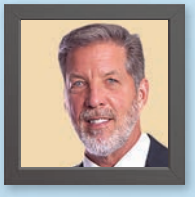
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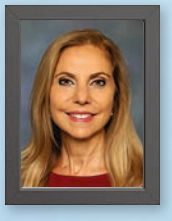
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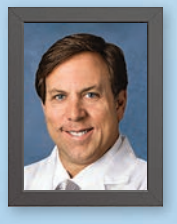
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