Wills Eye Resident Series: Years After LASIK, a Patient Presents with an Injury to His Right Eye, *p 70*

REVIEW® of OPHTHALMOLOGY

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THE CUTTING-EDGE PRACTICE

Surgeons discuss the pros and cons of novel concepts and technology.

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

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

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

Indication

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

Important Safety Information

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

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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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Genetic Evidence Strengthens Link of Smoking, Alcohol to AMD

The global health burden of age-related macular degeneration is projected to grow rapidly in the next two decades, due to the aging population. However, "The treatment for neovascular AMD is expensive and only sometimes effective," says Valerie Kuan, PhD, of the Institute of Health Informatics, University College London. "There's also no cure for the AMD subtype geographic atrophy." She and her colleagues say that public health efforts directed toward prevention will be critical.

They recently published a study in *JAMA Ophthalmology* that provides genetic evidence that smoking and alcohol are associated with advanced AMD.[1] "This lends strength to the premise that these risk factors may be causal for AMD," she says.

The study employed a method called Mendelian randomization (MR), which Dr. Kuan explains, "is a method of using the association in the level of an exposure variable with genetic variants to examine the causal effect of a modifiable exposure on disease in observational studies."

It's based on a version of the transitive property of equality, where if a certain genetic variant causes a change in exposure to something that is causal for a disease (such as tobacco use), then that genetic variant is associated with the risk of disease.[1] Genetic variants are used as natural experiments.[2] They make good instrumental variables on the assumption that they associate with the risk factor; that they're not related to confounders; and that they affect the outcome only through the risk factor.[2]

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Mendelian randomization is particularly suited for identifying causal associations in age-related diseases such as macular degeneration, where exposure to risk factors and clinical manifestations of the disease may be separated by several decades. The method helps to reduce confounding or reverse causation and is more cost-effective than large-scale randomized clinical trials. It also steps in where RCTs fall short—it's just not possible to conduct an RCT to pinpoint whether a specific exposure such as alcohol consumption is an actual modifiable risk factor.[1,3] (For more information on MR, Dr. Kuan recommends a *BMJ* podcast that interviews the authors of a paper on reading and assessing MR studies for clinicians. Both can be found at bmj.com/content/362/bmj.k601.)[2]

Dr. Kuan's study used two-sample MR, which further increases statistical power and allows for the use of very large datasets.[2] From published genome-wide association studies, she and her team obtained genetic instruments composed of variants associated with AMD risk factors at genome-wide significance ($p<5x10^{-8}$). They obtained summary-level statistics for the instruments for advanced AMD from the International AMD Genomics Consortium 2016 dataset, which included 16,144 subjects with AMD and 17,832 controls.

The researchers performed univariable inverse-variance-weighted two-sample MR analyses under a multiplicative random-effects model to assess the potential causal role of several exposures, including smoking, alcohol intake, body mass index, blood pressure and glycemic traits, on advanced AMD and its subtypes geographic atrophy and nAMD. They also performed multiple sensitivity analyses. Here are the key findings of the study:

- Genetic predisposition to starting smoking was associated with higher risk of advanced AMD (odds ratio [OR], 1.26; 95% CI, 1.13 to 1.4; $p<0.001$). They reported a similar association with nAMD (OR, 1.26; 95% CI, 1.11 to 1.43; $p<0.001$) but not with geographic atrophy (OR, 1.24; 95% CI, 1.03 to 1.49; $p=0.02$).
- Genetic predisposition to stopping smoking was associated with lower levels of advanced AMD than continuing to smoke (OR 0.66; 95% CI, 0.5 to 0.87; $p=0.003$).
- Genetic predisposition to lifetime

(Continued on p. 8)

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Genetics and AMD

(Continued from p. 5)

smoking (measured by a composite index that accounted for smoking status, duration, heaviness and cessation) was associated with a higher risk of advanced AMD (OR, 1.32; 95% CI, 1.09 to 1.59; p=0.004).

• Genetic predisposition to higher alcohol consumption was associated with increased risk of geographic atrophy (OR 2.7; 95% CI, 1.48 to 4.94; p=0.001) but not with nAMD. The researchers say further studies are needed to find out why this is.

• They found no evidence that BMI, blood pressure, type 2 diabetes, HbA1c, fasting glucose level or fasting insulin level had a causal association with AMD risk.

"A large number of observational studies have shown an association between smoking and AMD, which we've confirmed in this study," Dr. Kuan notes. "However, the evidence for alcohol has been less consistent. We've shown here a link between alcohol and geographic atrophy, which is important because there's currently no cure for GA."

Oxidative stress and damage are thought to be the mechanisms by which alcohol affects the retina. Alcohol depletes antioxidant levels and promotes production of reactive oxygen species.[1] However, in moderation, it's been reported to have some protective effects for AMD through decreased platelet aggregation, lower serum fibrinogen, C-reactive protein levels and increased high-density lipoprotein cholesterol levels.[3]

The study was limited by a relatively small dataset (e.g., compared to cardiovascular disease), which may have impacted its statistical power, even though it used the largest known advanced-AMD genome-wide association studies. Additionally, the estimates from MR studies must be interpreted carefully.[1] Because genetic variants refer to lifelong differences in a risk factor, not effects of a clinical intervention at a specific point in time,[2] the MR estimate is better interpreted as a test statistic for a causal hypothesis.[1]

What should clinicians tell their patients? "The message is prevention, not cure," says Dr. Kuan. "It's preferable to abstain from smoking (or stop smoking if you've started) and drink less alcohol if you want to lower your risk of developing AMD. Public health bodies should certainly be raising awareness that in addition to smoking leading to cancers and cardiovascular disease, and increased alcohol intake leading to liver damage, both of these activities can also lead to blindness. For some people, this might be a stronger deterrent."

1. Kuan V, Warwick A, Hingorani A, et al. Association of smoking, alcohol consumption, blood pressure, body mass index, and glycemic risk factors with age-related macular degeneration: A Mendelian randomization study. JAMA Ophthalmology 2021. [Epub November 4, 2021].
2. Davies NM, Holmes MV, Smith GD. Reading Mendelian randomisation studies: A guide, glossary, and checklist for clinicians. BMJ 2018;362:k601.
3. Su X, Wong T. Revisiting the alcohol consumption association with age-related macular degeneration: What should we tell patients in 2021? JAMA Ophthalmology, Invited Commentary 2021. [Epub November 4, 2021].

The Blood Pressure/Glaucoma Connection

To assess the relationship between blood pressure and glaucoma, and learn whether or not medications play a part, researchers recently conducted a retrospective cohort study of a National Institutes of Health electronic health records database.[1] They pointed out that the program is uniquely suited to studying glaucoma risk factors, as it offers comprehensive, longitudinal health information for more than a quarter of a million patients in the United States. They included patients with at least 15 months of follow-up and one BP measurement.

A total of 20,815 patients qualified for the study; of these, 462 developed OAG. The researchers reported that low BP, defined as mean arterial pressure (MAP) lower than 83 mmHg, was associated with an increased risk of developing OAG. High BP (MAP >101.3 mmHg) and the number of BP medication classes, on the other hand, weren't associated with OAG after the researchers adjusted for covariates.

They also reported elevated risk among those who were Black, Hispanic, Latino, Asian, older and/or diabetic. Additionally, female sex was associated with a decreased risk of OAG development. They noted no significant interaction between arterial pressure and the number of BP medications on the risk of OAG development.

The researchers noted that though MAP didn't differ significantly between patients who developed OAG and those who didn't, its effect on OAG development was significant after controlling for confounding factors. "Increasing the number of BP medication classes appeared to be associated with increased hazard of developing OAG until other factors were adjusted for in multivariable regression," they said. "These results suggest that all other factors being equal, lower BP is associated with increased risk of developing incident OAG."

Other studies, such as the Rotterdam Study, Egna-Neumarkt Study and Beaver Dam Eye Study, have noted a positive association between hypertension and increased IOP, but they haven't demonstrated a corresponding increase in development of open-angle glaucoma. "These

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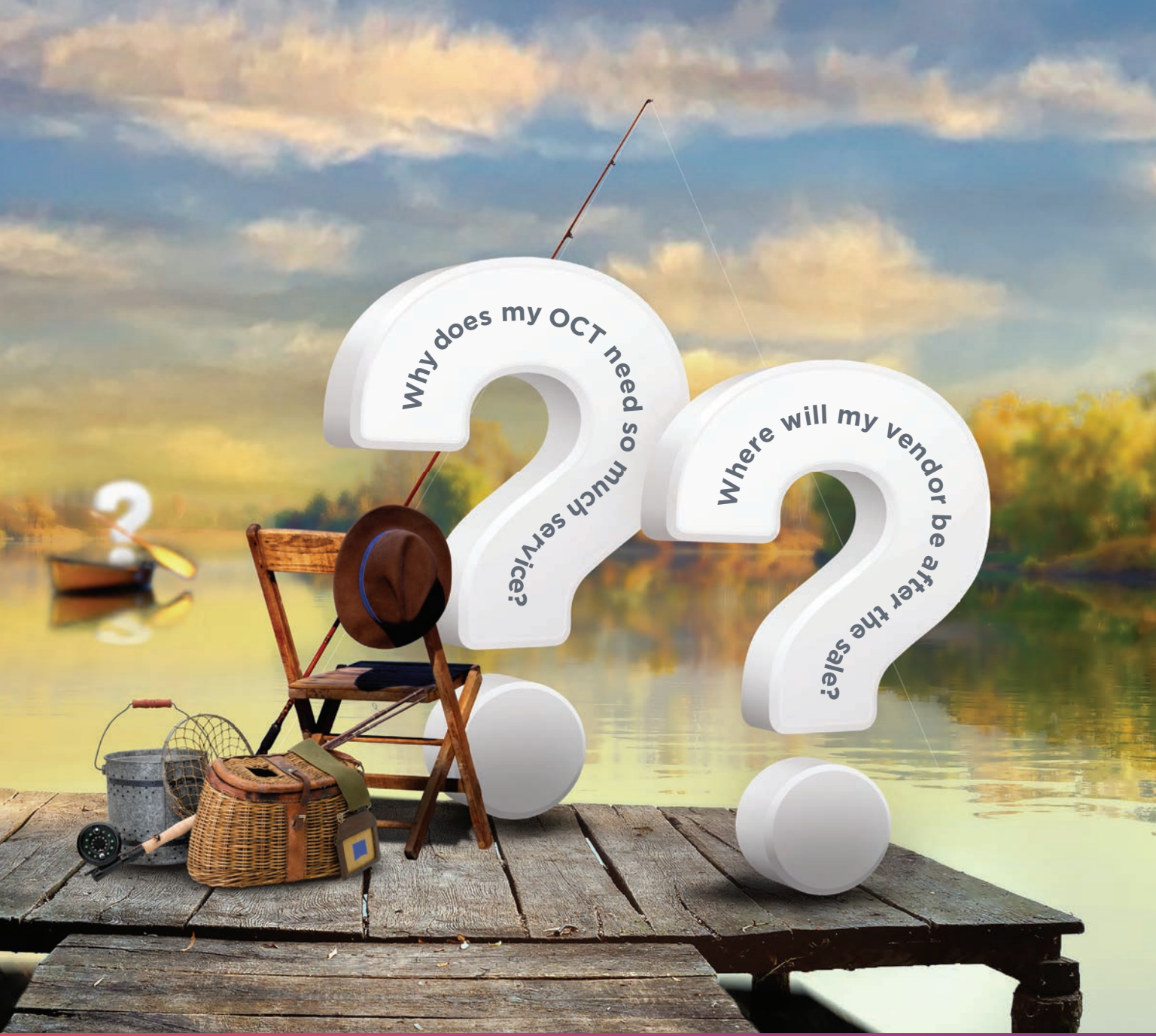

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Please see next page for Important Product Information and supporting references.

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References: 1. Alcon Data on File. **2.** Kohnen T, Mathys L, Petermann K, et al. Update on the comparison of femtosecond laser-assisted lens surgery to conventional cataract surgery: a systematic review and meta-analysis. Paper presented at: ESCRS; October 7-11, 2017; Lisbon, Portugal. **3.** Kranitz K, Mihaltz K, Sandor GL, Takacs A, Knorz MC, Nagy ZZ. Intraocular lens tilt and decentration measured by Scheimpflug camera following manual or femtosecond laser-created continuous circular capsulotomy. *J Refract Surg.* 2012;28(4):259–263. **4.** Ali MH, et al. Comparison of characteristics of femtosecond laser-assisted anterior capsulotomy versus manual continuous curvilinear capsulorrhexis: a meta-analysis of 5-year results. *J Pak Med Assoc.* 2017;67(10):1574–1579. **5.** Mastropasqua L, Toto L, Mastropasqua A, et al. Femtosecond laser versus manual clear corneal incision in cataract surgery. *J Refract Surg.* 2014;30(1):27–33. **6.** Alcon Data on File. **7.** Crozafon P, Bouchet C. Real-world comparison of FLACS vs. standard PCS: a retrospective cohort study from an outpatient clinic in France. Poster presented at: ESCRS; October 7-11, 2017; Lisbon, Portugal. **8.** Al-Mohtaseb Z, et al. Comparison of corneal endothelial cell loss between two femtosecond laser platforms and standard phacoemulsification. *J Refract Surg.* 2017;33(10):708–712. **9.** Bouchet, C et al. Comparing the efficacy, safety, and efficiency outcomes between LenSx femtosecond laser-assisted cataract surgery and phacoemulsification cataract surgery: a meta-analysis. *Value in Health.* 2017;20(9):A800–A801. **10.** Yesilirmak N, Diakonis VF, Sise A, Waren DP, Yoo SH, Donaldson KE. Differences in energy expenditure for conventional and femtosecond-assisted cataract surgery using 2 different phacoemulsification systems. *J Cataract Refract Surg.* 2017;43:16–21. **11.** Roberts TV, et al. Update and clinical utility of the LenSx femtosecond laser in cataract surgery. *Clin Ophthalmol.* 2016;10:2021–2029. **12.** Roberts TV, Lawless M, Sutton G, Hodge C. Anterior capsule integrity after femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg.* 2015;41(5):1109–1110.

Open-angle Glaucoma Research

(Continued from p. 8)

studies were cross-sectional in design and couldn't measure the risk of developing incident OAG," the researchers note in their paper, published in *Ophthalmology*. "Furthermore, these studies were composed of ethnically homogenous populations, so it's unclear if their results can be broadly extrapolated to the general population."

Consistent with their study's findings, several longitudinal, population-based studies have identified an association between low BP and increased risk of OAG. These include the four- and nine-year follow-up data of the Barbados Incidence Study of Eye Diseases, which initially found a positive correlation with systolic BP and increased IOP, but upon further analysis of systemic hypertension, the study noted a negative association between hypertension and risk of OAG development. Also, the Early Manifest Glaucoma Trial's 11-year follow-up data showed that higher systolic BP (>160 mmHg) was protective against OAG progression.

The researchers say that, like the present study, the design of these previous longitudinal studies allows the measurement of incident glaucoma and identification of risk factors for incident glaucoma. They say that their results expand on the literature that points to systemic hypotension as a risk factor for incident open-angle glaucoma development.

Additionally, the researchers pointed out that this study is the first to examine the difference between therapeutically low and naturally low blood pressure on the risk of open-angle glaucoma development. "Since no significant interaction was identified between MAP and the number of BP medication classes on development of OAG, we didn't find that low blood pressure due to blood pressure medication use confers a different risk of developing OAG compared with naturally low BP.

"Like previous epidemiological studies," the investigators continue, "the associations described in this study don't provide conclusive evidence with regard to causation of glaucomatous disease, but rather add to the evidence supporting vascular risk factors as possible contributors to OAG pathogenesis. In the vascular dysregulation hypothesis of OAG, the relationships between BP, IOP and ocular perfusion pressure are implicated in adversely impacting ocular blood flow and thus damaging the optic nerve."

The researchers stress that although BP is a modifiable risk factor, the findings of their study "should by no means lead to a broad reduction in the treatment of hypertension in an effort to reduce glaucoma risk. The associated risk of incident open-angle glaucoma with hypotension, while statistically significant, would not likely outweigh the risks of uncontrolled hypertension. Further confirmation, including a better understanding of the pathophysiology of OAG, is necessary before adjustment of hypertension management for OAG prophylaxis can be considered." ◀

1. Lee EB, Wendeng H, Singh K, et al. The association between blood pressure, blood pressure medications, and glaucoma in a nationwide electronic health records database. Ophthalmology; October 21, 2021. [Epub ahead of print].

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REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

'Tis a Reason To Be Jolly

For most of us, our environment can have a strong influence on our attitudes and outlook, both for good and ill. For instance, it's easy to have a bright and sunny disposition on a beautiful day in June, but it's a lot harder in winter when it's already dark at 4:45 p.m., and you're trudging through an ice storm.

It's ironic, then, that the period of the year that's filled with the most darkness and cold weather (at least here in the Northeast) is often home to the warmest, most friendly feelings. Seasonal songs exhort everyone to be of good cheer and celebrate "good will toward men." Families and friends gather to spend valuable time with each other, and maybe exchange gifts. There's a general air of optimism and hope, despite the weather and lack of sun.

This line of thinking is interesting when you consider some of the sentiment expressed in our article on in-office cataract surgery, part of our cover focus on novel techniques and technologies ophthalmology practices may incorporate in the coming years. At one point in the article, Omaha surgeon Lance Kugler notes how, in past decades, when surgeons' approach to cataract surgery changed, it was a crisis that made people wonder how the profession would emerge from it.

"[Cataract surgery in the early 80s] was a big deal and required general anesthesia," says Dr. Kugler. "When surgeons started to perform outpatient cataract surgery, people thought it was crazy. People were actually disciplined by hospital boards for sending patients home after cataract surgery. But, after a while, everyone realized that it made sense and that it was good for payers, patients and surgeons, so they continued to do outpatient surgery in the hospital." In fact, after the initial wave of concern over outpatient cataracts, the Health Care Financing Commission actually ruled that all cataracts should be removed in an outpatient facility, save for those patients with "exceptional circumstances."

Please note that this isn't a call for in-office surgery, since it's not without its issues (also noted in the article). Instead, I'm illustrating how, even in trying times, ophthalmologists have found ways to make new approaches work for both their profession and their patients. They've found some hope when things appeared dark.

Likewise, during this period of declining reimbursements, hopeful signs may be appearing from an unexpected quarter: Recent estimates put refractive surgery on pace for a 16-percent increase in volume compared to last year.[1] Though this increase will need to be sustained, of course, this renewed interest in refractive surgery might also signify the renewal of a potentially significant income stream for ophthalmology practices scrambling after each fresh reimbursement cut.

With these hopeful thoughts in mind, the staff here at *Review* would like to wish you and yours a happy and healthy holiday season.

— Walter Bethke
Editor in Chief

1. Demand for Laser Vision Correction Procedures Increases During COVID-19 Pandemic. https://americanrefractivesurgerycouncil.org/press-room/demand-for-laser-vision-correction-procedures-increases-during-covid-19-pandemic/. Accessed November 29, 2021.


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Suturing a One-Piece Lens In Place

A surgeon describes two new techniques that may allow safe fixation of a one-piece lens in a problematic eye.

CHRISTOPHER KENT
SENIOR EDITOR

Dealing with a malpositioned intraocular lens is always a challenge. Nevertheless, there are multiple options for dealing with a malpositioned three-piece IOL, including scleral and iris fixation. That's not the case when the dislocated lens is a one-piece lens. In that situation—especially if the haptic is exposed—many surgeons would opt to remove the lens and replace it.

Recently, Kenneth J. Rosenthal, MD, FACS, an associate professor of ophthalmology at the John A Moran Eye Center, University of Utah, and surgeon director at Fifth Avenue Eye Care and Surgery/Rosenthal Eye Surgery in New York, developed two new techniques for suturing a one-piece lens in place that appear to be safe and effective. Here, he shares how he proceeds when faced with this type of scenario.

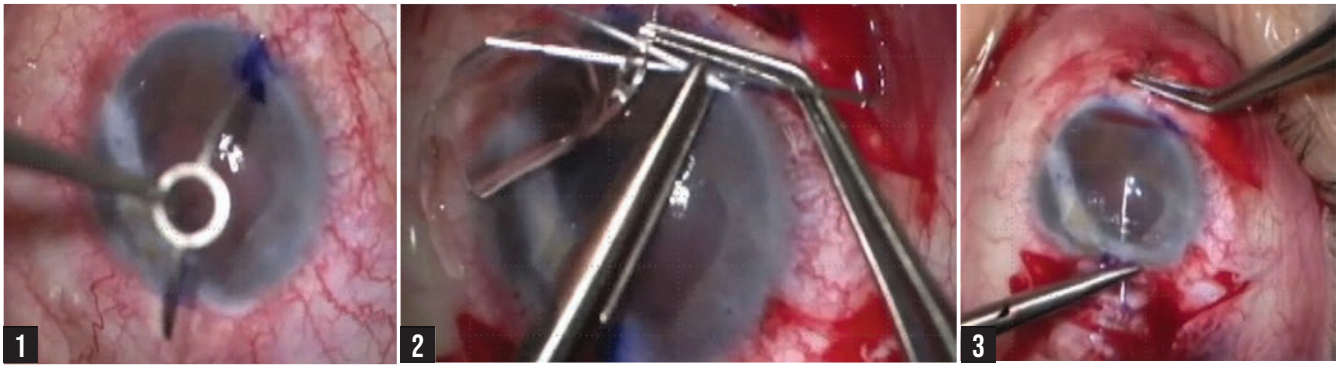
The Problem

"If the patient has a malpositioned one-piece lens, it's usually a bad idea to place it in the sulcus, where you could end up with apposition and resulting chafing between the haptics of the one-piece and the posterior iris," Dr. Rosenthal says. "When deciding how to deal with this, it matters whether the haptic is exposed. If it's a dislocated capsular bag/lens complex—in other words, if the lens and haptics are still within the capsular bag, but the zonules have let loose—then you can lasso the haptic and pull it in.

"On the other hand, if it's a bare haptic, it has to be handled differently," he continues. "If you have a one-piece lens that's been dislocated with the haptic exposed, that lens would normally be explanted, to avoid contact between the haptic and the posterior iris. You can't just lasso it and suture it using standard techniques, because the likelihood of it rubbing on the back of the iris is too great.

"However, there are cases in which there's a compelling reason to leave the lens in the eye, such as when it's a toric lens," he notes. "In the United States, at least, all toric lenses are one-piece acrylic. If you remove a toric lens and replace it with a spherical lens, the patient will be left with all the astigmatism the lens was correcting.

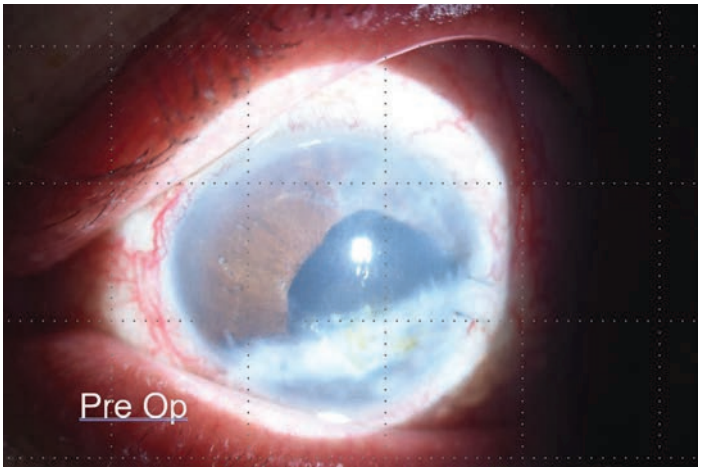
"For that reason, I've developed two surgical techniques for fixating the haptic in this situation—not previously published but presented at national meetings—in which the

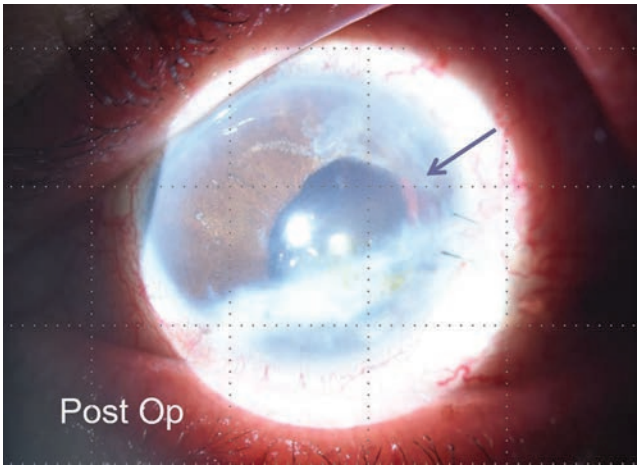


This patient, who had a previous penetrating injury, developed endophthalmitis following implantation of a toric lens. A vitreoretinal surgeon removed the lens, leaving the patient with high astigmatism. Because a corneal scar made treating the astigmatism at the cornea impossible, the original surgeon decided to replace the lens and suture the new one in place, using a new technique. 1) Marking the steep axis for the astigmatism. 2) Forceps hold the haptic of the new toric lens while two needles (for a double-armed 9-0 prolene suture) are passed through it. 3) The suture is passed across the eye and pulled out through a scleral groove placed 2 mm behind the limbus.

This article has no commercial sponsorship.

Dr. Chayet is considered a pioneer in refractive and cataract surgery, and is the medical director of the Codet Vision Institute in Tijuana, Mexico. He is a clinical investigator for RxSight, LensGen and ForSight Vision6. **Dr. Rosenthal** has no financial interest in any products mentioned.





The eye shown in the series on the facing page, before and after the procedure. The arrow points to the toric lens alignment marks.

lens is repositioned with the haptic fixated to the scleral wall posterior to the iris, making sure that there's no iris-haptic contact," he explains. "This can be done using either of two techniques."

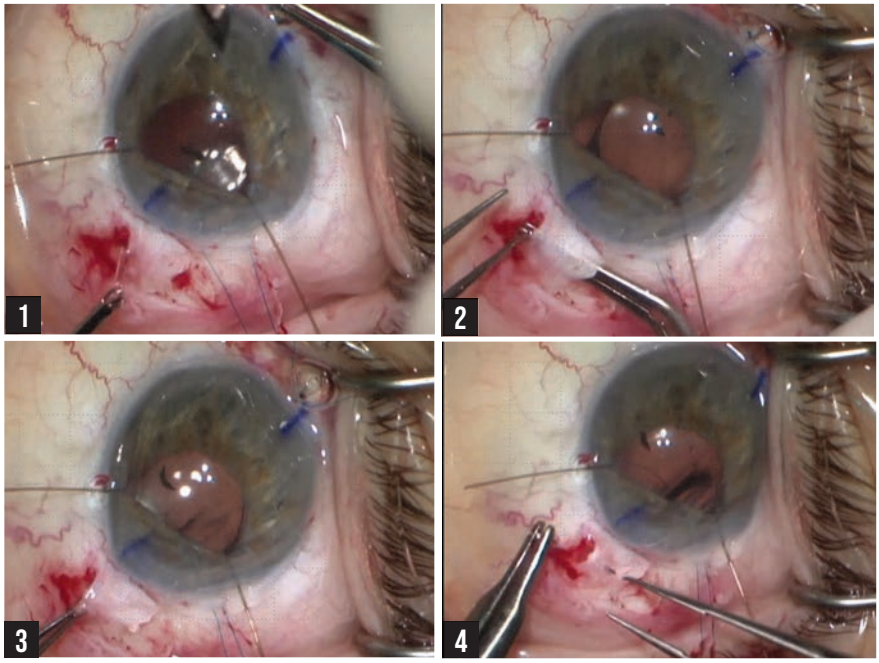
The Two Techniques

Dr. Rosenthal explains that the first technique involves passing a suture—usually a polypropylene suture on a long, curved needle—through the haptic itself. "Most haptics are thick enough that you can actually pass the suture through the parenchyma or substance of the haptic," he points out. *(See photos, facing page.)* "Then, you fixate the haptic in the posterior part of the ciliary sulcus, typically about 2.5 mm behind the limbus, inspecting it carefully to make sure there's no contact with the iris. You can do this with an intraocular endoscope or an intraocular UBM.

"The second technique involves a modified Yamane-style fixation of the one-piece lens," he continues. "In standard Yamane, you withdraw the haptic to the scleral surface through the barrel of a 30-ga. thin-walled needle; with my modified one-piece technique, you make a 1-mm intrascleral groove and reach in and grasp the haptic and pull it out. Then you pass a suture through the haptic and then the sclera. *(See photos, right.)* Using this technique, we know where the haptic is, and it's away from the back of the iris. (I've designed an instrument specifically for reaching in and grasping the haptic that's not yet in production, but should be soon.)

"I'm aware that this technique is controversial," he notes. "Some surgeons have misunderstood this as being the same as leaving the haptic in the sulcus without fixation. That's not recommended because of the potential for the haptic to cause uveitis, pigment loss and so forth. However, this approach is very different from that. In fact, I have successful five-year follow-up on a small case series in which I used this technique.

"Incidentally," he adds, "when using this technique the fixation of the toric lens is absolute. A toric lens can rotate inside a capsular bag. That's one of the potential issues with these lenses, although the newer designs make rotation less likely. But when you fixate the lens with a suture, the lens is locked in position—it won't move a micron."



External one-piece haptic fixation. 1) The haptic is pulled out through the sclera. 2) The surgeon has created a scleral sleeve and grabs the haptic. 3) The haptic has been pulled through the sleeve; the end of the haptic can be seen sticking out. 4) A 9-0 prolene suture is passed around the haptic and through the sclera, securing the haptic in place.

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

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
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

God Bless Us, Every One

Musings on life, ophthalmology and the practice of medicine.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair."

How amazingly accurate Charles Dickens was about our last two years. This year was supposed to be a celebration of renewal, a return to normal, but we find ourselves at the end disappointed, disheartened and doubtful. Disappointed that we haven't wiped out COVID, disheartened that our profession continues to be under attack from insurers and regulators, and doubtful that a new year will bring us to a happier place.

Indeed, maybe it is the best and the worst. The stock market regularly hits all time highs and the vast majority of us have come out of 2021 relatively unscathed in our practices and our lives. However around us the world is changing and scary. We keep waiting for another shoe to drop in the pandemic, in the economy, in extreme weather.

Wisdom and foolishness. Credulity and disbelief. Fake news and alternative realities. I've written previously about the loss of absolute facts, the unmooring of our shared experiences. I suppose it's somewhat of a comfort to know it's happened before. It's been too easy this year, for reasons medical and political, to find ourselves sitting in dark corners with sharp sticks aimed outward, angry and afraid of each other in turns.

At year's end, when we've seen and experienced so much, it's difficult to settle down and celebrate. But I would submit that at this time of year in particular, we should take stock of our blessings and what we have rather than what we don't have. Let's not focus on what could have been, but on the important things that seem to get lost in the chaos of modern life: our families, our friends, our colleagues, our patients.

So many of my columns this year have been a bit heavy … and depressing (or at least unsettled). I've always felt that the December holidays, whichever ones you celebrate, should be a time of optimism and happiness, no matter the situation. And so, in this, my last musing of the year, its time to make an effort to get beyond the isolation, the echo chambers and the bubbles our lives have become, and reach out to each other. Let's focus on what brings us together, what makes us happy and, most importantly, on what's important, so that we close out this year not with dread or worry but with warmth, camaraderie and an appreciation for all that we have. Even though Charles Dickens documented a dystopian world that never seems to go away, he also gave us hope in the form of a small child at Christmas, wishing all of us a better day to come. ◀

This article has no commercial sponsorship.

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

Reference Apps For Ophthalmologists

Five smartphone apps that can save you time and bring some peace of mind.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

While search engines are useful, sometimes it's nice to have a dedicated, doctor-vetted app to look up what you need.

Here are five reference apps developed by doctors to consider downloading.

Acronym Help

"Ophthalmology uses acronyms in our documentation and notes probably more than any other field," says OE Acronyms (Ophthalmic Edge) co-director Grayson Armstrong, MD, MPH, a comprehensive ophthalmologist and medical director of Ophthalmic Emergency Services at the Massachusetts Eye and Ear Infirmary. He presented the app at the Retina Society meeting in Chicago. He works on the program alongside Nimesh A. Patel, MD, a pediatric and adult retina specialist at Mass EE and app creator Yale L. Fisher, MD, of Vitreous Retina Macula Consultants of New York. Dr. Fisher founded Ophthalmic Edge as a 501(c)(3) nonprofit.

"This app can help nurses, internal medicine doctors, technicians, medical students, patients and others who might not understand the language of what we do in our field," he explains. "Misunderstanding certain acronyms can be dangerous. Take ICP, for example. In internal medicine and neurology, this means intracranial pressure. In ophthalmology, it's intermediate capillary plexus for uveitis. Even within ophthalmology, not all subspecialists are familiar with the acronyms of other subspecialities. This limits our ability to provide team-oriented care."

OE Acronyms is a free, open-source app that currently includes more than 2,600 ophthalmic acronyms. The developers say it helps to prevent confusion among those who aren't familiar with the many acronyms ophthalmic subspecialties use.

Dr. Grayson says the Cares Act, which gives patients access to their records and notes, has also introduced the potential for patients to misunderstand ophthalmic acronyms. "This may lead to their taking the wrong medication or the wrong dosage or thinking they need a certain treatment," he says. On a lighter note, he points to the acronym PEE, punctate epithelial erosion. "It's a common finding, but patients get confused, thinking we're talking about pee in their eye."

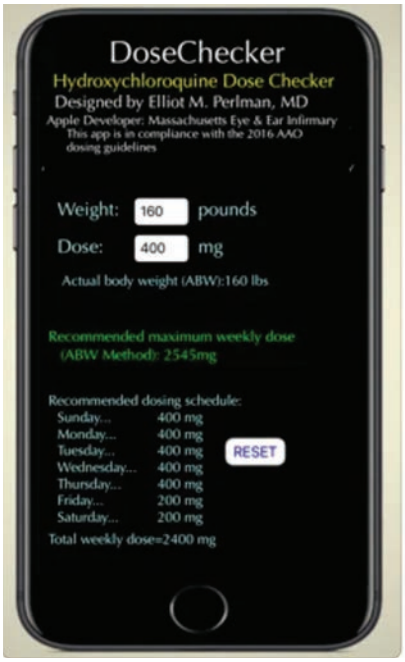
The free, open-source app covers all subspecialties of ophthalmology and currently includes more than 2,600 acronyms. It had 1,152 users as of September and more than 63 contributors. "Anyone can contribute an acronym," says Dr. Armstrong. "In the online form, you put in the acronym, provide a short description, and then add your name as a contributor. We want to give people credit for their work, as well as ensure it's a legitimate acronym from a legitimate individual."

The app also includes major clinical studies' acronyms, such as MARINA, PIVOT and HARRIER. "There's a brief description of each trial's key findings," says Dr. Armstrong. "You can save favorite acronyms and trial nicknames and make flashcards to study."

When searching for an acronym, users can search by the letters or by the clinical findings or diagnosis. Each acronym and definition are categorized by subspecialty, so users

This article has no commercial sponsorship.

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



DoseChecker offers hydroxychloroquine dosing recommendations in a weekly schedule using a combination of 400-mg and 200-mg daily doses because the drug is available only in 200-mg tablets.

also have the option of looking only at the oculoplastics acronyms or only at the retina acronyms, for example.

Dr. Armstrong says he uses the app most often during grand rounds. "There are a lot of acronyms being thrown around by ophthalmic subspecialists," he says. "I can look them up quickly. It's also convenient for technicians. My techs do all the workup and intake for my patients, but I'm a comprehensive ophthalmologist, so they don't often see a lot of things for retina, glaucoma or cornea in my notes. They can look up the acronyms on their phones to check what testing or work-up needs to be done before the patient sees me. It helps streamline the clinic." OE Acronyms is available for Android and iPhone. For more information, visit oeacronyms.com.

Plaquenil Dosing

DoseChecker from the Massachusetts Eye and Ear Infirmary is an app that helps clinicians determine a safe dosing regimen for hydroxychloroquine. The current version of the app uses only Absolute Body Weight to calculate dosing toxicity, in accordance with the 2016 AAO guidelines. According to this method, which assumes the drug is distributed evenly throughout muscle, skin and fat, the maximum daily dose is 5 mg/kg/day x ABW (kg).[1]

Long-term use of hydroxychloroquine puts patients at increased risk for developing hydroxychloroquine retinopathy. The app provides an adjustable weekly dosing schedule using a combination of 400-mg and 200-mg daily doses, since the drug is available only in 200-mg tablets. Dosing recommendations are always within the approved drug labeling and for use only by clinicians, which obviates the need for FDA regulation as a class I mobile medical device.[1] In the published paper on the app, the creators say prescribing doctors should consider cumulative dose, concomitant retinal disease and presence of systemic disease, which may affect a patient's risk for developing toxicity.[1] Additionally, ophthalmologists should refer to the AAO recommendations for screening and follow-up. DoseChecker is available in the App Store.

Virtual Call Bag

You've probably heard of Eye Handbook (Cloud Nine Development), or maybe even have it on your phone. It's one of the most downloaded eye-care apps, and it has a host of features, including vision-testing tools, various calculators, an atlas of eye images, a collection of educational videos, a coding tool and a new online forum.[2]

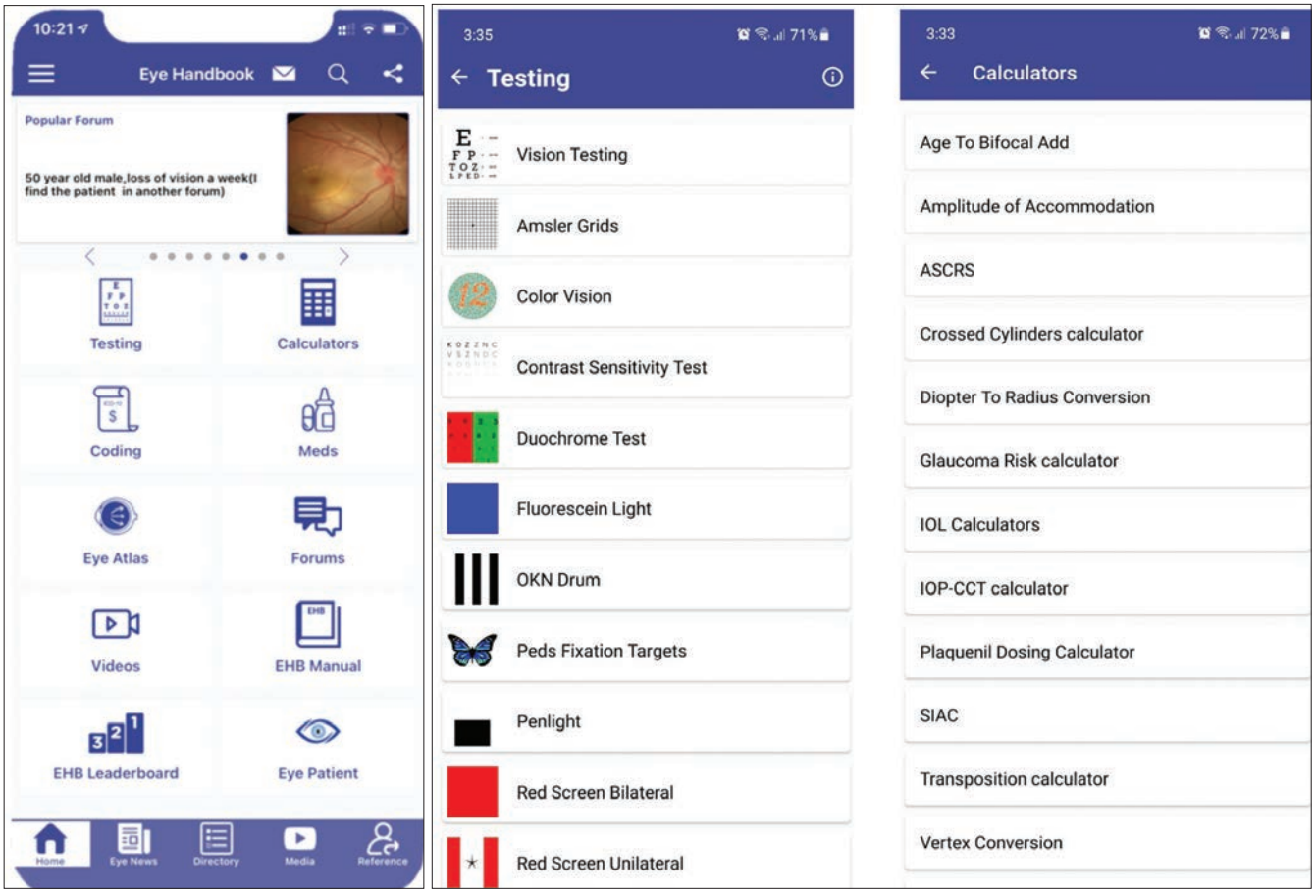
Vinay Shah, MD, a vitreoretinal specialist and clinical associate professor at Dean McGee Eye Institute, University of Oklahoma College of Medicine, created the app with Ken Lord, MD, of Retina Associates of Southern Utah, when they were residents at the University of Missouri Kansas City.

The eFACE app from Massachusetts Eye and Ear Infirmary helps clinicians identify facial palsy. It performs static readings, dynamic movement readings and synkinesis scores, and can be used to obtain clinician-rated scores for 16 separate facial function features.

Rohit Krishna, MD, director of the glaucoma service at UMKC School of Medicine, is also a partner.

"It's kind of like a one-stop shop," Dr. Shah says. "It's eye-care-facing, but many emergency room doctors, primary care doctors and neurologists use the app as well. Some patients use it to test their own vision. I use the vision-testing tools whenever I'm doing consults or seeing patients in the emergency room. I don't have to carry around a bunch of different charts." He also frequently refers to the BMI and Plaquenil dosing calculators, as well as the coding feature.

"We update the content once or twice a month," he explains. "The Eye Atlas images are contributed from other doctors or from us. We also curate the educational videos mainly from YouTube, so they're all in one place. The Forums are useful for sharing cases or getting some



Eye Handbook is a comprehensive tool that includes educational material, an online forum, an atlas of eye images and coding information.

ideas from other doctors. There's a built-in media consent for sharing images, but users should also check the consent requirements unique to their institutions." Eye Handbook is available for Android and iPhone. For more information, visit eyehandbook.com/EHBweb.

Facial Palsy Detection

Two new online resources can help detect facial palsy. The eFace (Massachusetts Eye and Ear Infirmary) app is a digital, clinician-graded facial function scale that provides quantitative and graphic depictions of facial function scores in patients who suffer from unilateral facial paralysis. It performs static readings, dynamic movement readings and synkinesis (misrouting) scores, and can be used to obtain clinician-rated scores for 16 separate facial function features. In studies, it's been well-received by facial nerve experts[3] and has demonstrated reliable, reproducible and straightforward digital clinical measures for assessing facial paralysis.[4] It's available in the App Store for $9.99.

There's currently no standardized assessment of facial palsy, however, and clinician-graded scales like the eFace are still subjective and limited by observer bias. One proposed way to move toward conformity in grading is by using artificial intelligence. Researchers at the Massachusetts Eye and Ear Infirmary and the Florida Institute of Technology's biomedical engineering program developed a machine-learning program called auto-eFace and compared it to the eFace. They found that the auto-eFace predicted more asymmetry in normal patients and less asymmetry in patients with flaccid palsy and synkinesis, compared to clinician grading.

In the study, clinician-graded eFace assessment was performed on 160 photographs from the center's Standard Facial Palsy Dataset, and a Python script was used to generate auto-eFace scores on these same photographs. Auto-eFace produced significantly lower scores than the eFace for normal faces (93.83 ±4.37 versus 100 ±1.58, p=0.01). The machine-learning program reported better facial symmetry in patients with flaccid paralysis (59.96 ±5.8) and severe synkinesis (62.35 ±9.35) than clinician-graded eFace (52.2 ±3.9 and 54.22 ±5.35, respectively, p=0.080 and p=0.080, respectively). The Auto-eFace software is available online for free.

Smart Coding

"SeePT is a licensed app that takes the CPT codes applicable to ophthalmologists and puts them in an accessible, searchable form that allows intelligent searches based on

IN THE BATTLEGROUND OF DRY EYE...

When Dry Eye Flares strike, fight back first with fast.

- EYSUVIS is ***THE FIRST AND ONLY FDA APPROVED SHORT TERM (up to two weeks) RX TREATMENT*** for the signs and symptoms of Dry Eye Disease
- EYSUVIS ***RAPIDLY REDUCED**** Dry Eye signs and symptoms in the largest clinical development program in Dry Eye (N=2871)[1]
- EYSUVIS ***TARGETS OCULAR SURFACE INFLAMMATION***, an underlying pathology of Dry Eye
- EYSUVIS is formulated with AMPPLIFY® Drug Delivery Technology, designed to ***ENHANCE OCULAR SURFACE TISSUE DISTRIBUTION AND PENETRATION***[2,3]
- EYSUVIS had a ***LOW INCIDENCE OF INTRAOCULAR PRESSURE ELEVATION*** (similar to vehicle) and was well-tolerated in clinical trials[4] —Please see Warning on Intraocular Pressure Increase below

*The safety and efficacy of EYSUVIS was assessed in 4 multicentered, randomized, double-masked, placebo-controlled trials in 2871 patients with documented Dry Eye. Patients received either EYSUVIS or vehicle 4 times a day for at least 2 weeks. Patients taking EYSUVIS showed significant reduction in the symptoms of Dry Eye (ocular discomfort) as early as Day 4 after starting treatment (versus vehicle). Symptoms continued to improve up to the end of the treatment period (Day 15). Patients taking EYSUVIS also showed significant reduction in signs of Dry Eye (conjunctival hyperemia) at Day 15 versus vehicle.

EYSUVIS®
(loteprednol etabonate ophthalmic suspension) 0.25%
THE FAST FLARE FIGHTER

INDICATION

EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

IMPORTANT SAFETY INFORMATION

Contraindication:

EYSUVIS, as with other ophthalmic corticosteroids, 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.

Warnings and Precautions:

Delayed Healing and Corneal Perforation: Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining.

Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP

Cataracts: Use of corticosteroids may result in posterior subcapsular cataract formation.

Bacterial Infections: Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, corticosteroids may mask infection or enhance existing infection.

Viral Infections: Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular corticosteroids 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 coincidentally with long-term local corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration where a corticosteroid has been used or is in use.

Adverse Reactions:

The most common adverse drug reaction following the use of EYSUVIS for two weeks was instillation site pain, which was reported in 5% of patients.

Please see Brief Summary of Prescribing Information for EYSUVIS on the next page.

References: 1. Holland E, Nichols K, Foulks G, et al. Safety and efficacy of KPI-121 ophthalmic suspension 0.25% for dry eye disease in four randomized controlled trials. Presented at: AAO 2020: November 13-15, 2020; virtual meeting. **2.** Schopf L, Enlow E, Popov A, et al. Ocular pharmacokinetics of a novel loteprednol etabonate 0.4% ophthalmic formulation. *Ophthalmol Ther*. 2014;3(1-2):63-72. **3.** Popov A. Mucus-penetrating particles and the role of ocular mucus as a barrier to micro- and nanosuspensions. *J Ocul Pharmacol Ther*. 2020;36(6): 366-375. **4**. Korenfeld M, Nichols KK, Goldberg D, et al. Safety of KPI-121 ophthalmic suspension 0.25% in patients with dry eye disease: a pooled analysis of 4 multicenter, randomized, vehicle-controlled studies. *Cornea*. 2020. In press.

kala PHARMACEUTICALS

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

CONTRAINDICATIONS

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Fungal Infections—Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate.

Risk of Contamination—Do not to allow the dropper tip to touch any surface, as this may contaminate the suspension.

Contact Lens Wear—The preservative in EYSUVIS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of EYSUVIS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS

Adverse reactions associated with ophthalmic corticosteroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

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.

The most common adverse reaction observed in clinical trials with EYSUVIS was instillation site pain, which was reported in 5% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy—Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 1.4 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 34 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 3.4 times the RHOD. Maternal toxicity was observed in rats at doses 347 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 34 times the RHOD.

The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data—*Animal Data:* Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (1.4 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (5.6 times the RHOD). At 3 mg/kg (41 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (83 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.

Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (34 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (347 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (695 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (3.4 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg.

A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (3.4 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (34 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (347 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

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

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (174 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused pre-implantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (34 times the RHOD).

For a copy of the Full Prescribing Information, please visit www.EYSUVIS.com.

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Kala Pharmaceuticals, Inc.
Watertown, MA 02472

Part # 2026R02

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Kala®

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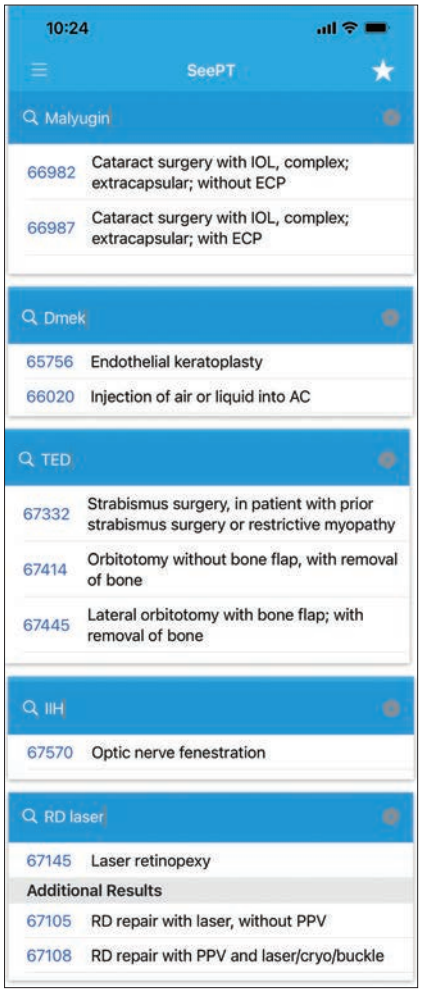

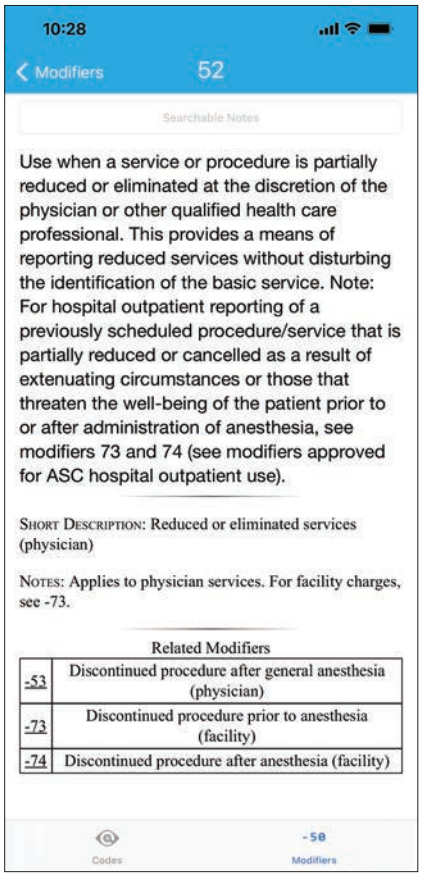

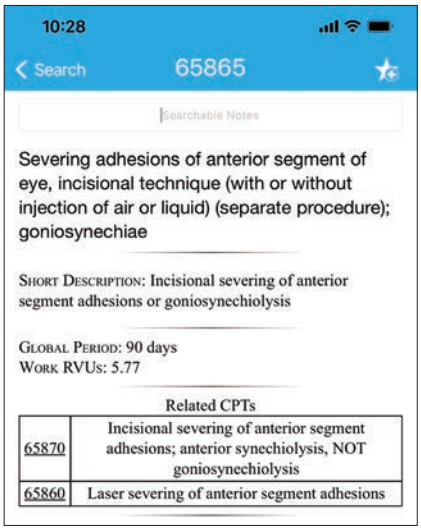

SeePT features smart-search technology that enables clinicians to quickly look up the codes they need using the natural language with which they think about the procedures.

the natural language ophthalmologists use to think about procedures," says developer Evan Schoenberg, MD, a cornea, cataract and refractive specialist in Atlanta. He and Evan Silverstein, MD, a pediatric ophthalmology specialist and an assistant professor in the department of ophthalmology at Virginia Commonwealth University, co-own a company called See Vision that develops medical apps.

What is smart coding? "It takes into account how ophthalmologists think," says Dr. Schoenberg. "If you were to search a database for the CPT code for cataract surgery and you typed in 'cataract,' you would eventually find the right code, but if you don't know the specific language used in the database, finding the right code becomes more difficult. For a simple example, say you're looking for the code that covers the use of a Malyugin Ring during cataract surgery. The official description of a complex cataract surgery—'requiring devices or techniques not generally used in routine cataract surgery (e.g., iris expansion device…'—doesn't include the words 'Malyugin Ring,' but the app knows to cross-reference 'Malyugin' and turn up the right code. A less common example might be for an implant procedure. Say you're doing a brand-name one like Dextenza. You may not realize it's listed in the database as a 'dexamethasone implant.'"

Dr. Schoenberg says that if you're using abbreviations, the system automatically expands them into familiar terms. "If you type in 'IOL' because you're doing an IOL exchange, you'll get the right code instead of having to guess the specific words used in the database."

The new CPT codes go live on the app for a seamless transition, so you're always using the most current version of the codes, Dr. Schoenberg explains. "The AMA requires a code license on a yearly basis. There's a free trial built into the app, which the AMA allows. Users will be notified when they need to license the new year's codes. If you choose not to, you'll still have access to the previous year's codes, but upgrading is recommended."

The yearly AMA code license is $24.99, which goes directly to the AMA. The smart search functions, RVU database and cross-referencing features of the app require a yearly subscription of $49.99. Dr. Schoenberg notes that purchasing the CPT code book, which doesn't include intelligent search functions, costs $85. "With the app, you have more function and convenience for less money," he says. "It pays for itself when you consider the ramifications of coding just one procedure incorrectly." SeePT is available in the App Store. For information, visit seevisionllc.com.

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OFFICE-BASED SURGERY: THE PROS AND CONS

Surgeons who are performing office-based cataract procedures say they're better for several reasons, but many physicians are still skeptical.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Office-based cataract surgery offers several benefits over procedures performed in an ambulatory surgery center, and some surgeons believe this practice will become more common in the next few years.

"From a big picture perspective, it's inevitable that we're going to be moving towards doing intraocular surgery in an office-based OR," says Omaha's Lance Kugler, MD. You have a situation where you've got something that's better for patients, for surgeons, and for third-party payers, and when those things align, it becomes inevitable that that's the direction things are going to go."

However, some surgeons are skeptical and are concerned about patient safety during office-based procedures. Here, both sides share their perspectives.

The Advantages of Office-Based Surgery

Jason Stahl, MD, who is in practice in Overland Park, Kansas, says his practice doesn't participate with insurance, but he has been providing in-office refractive lens exchange and refractive cataract surgery for almost two years. He mostly performs refractive lens exchange, and he does bilateral, simultaneous surgery. "It's been a really great addition to our practice because it's very similar to the LASIK encounters that we have with patients, where we walk them in, we do their surgery, and they walk out," he says. "It's very relaxed, and patients really enjoy having the procedure in our office. We occasionally have patients who have one eye done in an ASC and the other eye done in our office-based OR. All of these patients have commented that they preferred the office-based procedure. We are able to do the surgery with simply a little bit of Valium. No IVs are given. It's just very comfortable."

He adds that the main reason his practice decided to perform in-office IOL surgery was to better control the patient experience and to provide more of a LASIK-type experience for patients rather than going into a cold, sterile environment at an ASC. "We try to take it to the next level by doing it in the office," Dr. Stahl says.

Dr. Stahl had his doubts about whether the procedure could be done with just Valium and whether the patient would be able to just walk in and out. "Until I actually did it, it was kind of hard to believe," he says. "For 25 years, I've done my cases in an ASC, and it was hard for me to believe that we could simply give these patients 5 mg of Valium, walk them in, do the surgery and walk them out. But, then it made sense, because they're in a familiar environment. They're not on a bed being wheeled in and out. The patient already has less anxiety going into it than they would in an outpatient surgery center environment, and that's why they do so well with just very minimal sedation."

According to Dr. Kugler, there are cost benefits as well. "In-office procedures are less expensive for patients, too," he says. "ASCs were a wonderful invention because they brought costs down compared to hospitals, but there are a lot of costs to running an ASC that don't apply

This article has no commercial sponsorship.

Dr. Lindstrom is on the board of Minnesota Eye Consultants, UnifEYE Vision Partners and iOR Partners. **Dr. Durrie** is the chairman at iOR Partners. **Drs. Salz, Jarstad, Rosenthal** and **Frederickson** report no financial ties to any products discussed in their comments.

to ophthalmology. An in-office operating room that's designed only for eyes can improve your outcomes and safety standards relative to other centers. An office-based OR allows surgeons to maximize efficiencies in terms of time, schedule, staffing and supplies. And that's good for patients, surgeons and payers."

He adds that patients love having the procedure in the same facility where they see their surgeon. "I didn't really appreciate that this was going to be the case until we had our own in-office suite," he says. "For years, I went to an outpatient ASC across town. It was a really nice center with good equipment, and I thought it was comfortable for patients, but I learned that from the patient's perspective, it was a big deal because there was this new, third-party facility that they had never heard of or considered. This induced anxiety and a whole other layer of concern. Whereas, if we offer the procedure in our own center, patients are much more comfortable. They see the same staff that was there for their evaluation. The staff knows the patient, and they know if there's anything specific about them that we need to be thinking about. So, the overall experience from start to finish for the patient is much more comfortable. That's a big advantage."

Lance Kugler, MD

The in-office operating room in the practice of Omaha surgeon Lance Kugler.

The Cons

While proponents say there are many advantages to office-based procedures, they are not for all patients. According to Dr. Stahl, surgeons need to choose their in-office patients carefully. "If someone is very nervous, and we feel that he or she may need an IV, then we would want to do that procedure in an ASC," he says. "Certainly, patients with significant medical histories need to be done in an ASC, where nurse anesthetists are available if there are any issues. So, at least in our practice, in-office cataract procedures are for very healthy patients who we know will do well with very minimal sedation."

Kevin M. Miller, MD, who is in practice in Los Angeles, is concerned about patient safety and surgeon reimbursement. "The sole motivation behind this move from hospital outpatient department (HOPD)/ASC surgery to office-based surgery from the payer side, primarily driven by Medicare, is to reduce expenditures," he says. "Safety and quality are supposed to be givens in this thinking and should't be impacted by declining reimbursement, but everyone knows this isn't true. An overarching issue is that the Medicare trust fund will run dry in 2024, just three years from now, and those that administer it are desperate to reduce outlays. Cataract surgery is the number one procedure by volume in the United States. Medicare and private insurers have been reducing reimbursements for cataract surgery pretty much since Medicare was established in the mid-1960s, but now they're desperate."

He believes that there will be quality and safety risks for patients who undergo in-office cataract procedures. "You won't have an anesthesiologist, so if your patient is having issues such as pain or anxiety, there will be no anesthesiologist to call on to administer an intravenous solution," he notes. "If the sublingual anxiolytic or Valium that the patient took isn't doing the job, what are you going to do? You're not going to stop the surgery, put the patient in an ambulance, take him or her across town to the hospital, then finish up the procedure there. I believe safety will suffer. Medicare will counter that the routine cases can be done in the low-cost office environment and higher-risk patients can be done in an HOPD or ASC, which is better staffed. The argument is that there are plenty of clean cases around, but this isn't true. Virtually every patient in the cataract age range has ocular and systemic comorbidities and high-risk features or characteristics that put him or her at risk of intraoperative and postoperative complications. A high-risk feature might be a really dense cataract in a deep-set eye. Or, it might be that they have pseudoexfoliation or hearing difficulty. The list goes on and on. There are very few routine cases."

In the 1980s, when cataract surgery went from the inpatient to outpatient setting, surgeons had the same concerns. "People said it was bad for patients and there would be more systemic and ocular complications," says Dr. Miller. "However,

the switch was seamless, and the complications were no different. The switch didn't improve safety, but it didn't worsen safety. All of this was a huge benefit to Medicare in terms of cost savings. In fact, there are plenty of anecdotes of it actually being safer for patients because now they aren't stuck in a hospital bed where they can develop deep vein thrombosis or a pulmonary embolism. There might have been some actual benefit to getting them out of the hospital environment."

Dr. Miller says that, on top of all this, ophthalmologists are being squeezed now in a way that they were never squeezed before. "If it weren't for premium services, most cataract surgeons would have to close their doors," he avers. "Premium services are keeping the whole thing afloat. Cataract surgery has become a loss leader. Once you get a patient in the door for cataract surgery, you hope he or she will choose to add on some services, such as astigmatism management or a premium lens. You're going to receive even less reimbursement for in-office procedures, as compared to an HOPD or ASC procedure, but the supplies you will be required to maintain will be exactly the same. There is a financial risk for any practice that does this."

According to Dr. Miller, in the 1970s, Medicare paid about $2,400 for a cataract procedure, which would be about $7,000 today in a constant-dollars analysis. "But, our reimbursement is now less than $600," he says. "Reimbursements have gone down over 90 percent, while practice expenses have gone up at least threefold.

"I'm a skeptic that this is going to work, but we'll see," Dr. Miller continues. "I hate to be a naysayer. I'm optimistic about most things, but I don't see this working on a mass scale. Anecdotes will start coming out that this or that patient had a complication and that an ambulance had to be called."

According to Dr. Kugler, another con is that setting up your office and establishing protocols is difficult. "When we moved to an in-office suite," he says, "I had all of these same concerns: What about the anesthesia and the compliance protocols? It is important to make sure that you're setting it up with established protocols and that you have third-party accreditation. We hired a consulting group to do that for us. I think it's beyond the skill set of most individual surgeons to be able to set up an in-office OR without help." (*To learn more about how some practices are setting up in-office ORs, see "Defying Economic Gravity: 10 Ways to Boost Income" in the November 2021 issue.*)

The Evolution of In-office Surgeries

According to Dr. Kugler, there are many misconceptions about office-based surgery. "A lot of surgeons think there's just a procedure room in the corner where you're doing eye surgery," he says. "That's not the case at all. An office-based facility is a full operating room. It has the same or better standards as a hospital OR would have. There is a sterilization room, a clean room, a dirty room, air filtering, back-up power and everything else. It's literally a full OR. This is important to understand, because many people are picturing a backwoods set-up, and that's not what this is. The only difference is that your office doesn't have the ASC certification layer that goes on top of it. For example, our OR is certified by an independent third party, but it's not certified by Medicare. That's the difference."

In the early 1980s, patients typically stayed in the hospital for a week for cataract surgery. "It was a big deal and required general anesthesia," says Dr. Kugler. "When surgeons started to perform outpatient cataract surgery, people thought it was crazy. People were actually disciplined by hospital boards for sending patients home after cataract surgery. But, after a while, everyone realized that it made sense and that it was good for payers, patients and surgeons, so they continued to do outpatient surgery in the hospital. Then, it was later moved to outpatient surgery centers to save money for the system and also to make things better for patients and surgeons. But that was considered very renegade at the time. Then, surgeons went from general anesthesia to retrobulbar anesthesia to topical anesthesia, and each one of those changes was a major disruptor. Now, going from an ASC to an in-office operating room is a similar transition, and at the same time, we're going from monitored IV sedation to straight topical without any IV sedation. It's just kind of the natural evolution."

He adds that he has a nurse anesthetist in his practice about once a month, and he schedules all patients with medical conditions during this time. "If I have anybody who needs monitoring, I'll have an anesthesia provider there in the office," he notes. "I have that capability, but I never want to give patients more anesthesia than they need because I've learned that patients do better with less. They're more nervous and they jerk around [with more anesthesia], and it's much better to have less, which is very different than what I was taught during training, but that's what we've learned."

Dr. Kugler does more than 90 percent of his cataract procedures in his office, but there are rare instances in which he performs cataract surgery in an ASC or hospital. "If a patient has a large body mass index or if he or she needs to be transferred from a wheelchair, we don't have the staff with the training to handle those kinds of things, so I don't do those in my office," he says. "But that's very rare in my practice. Everything depends on your patient population and what percentage you can do in the office."

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TELEMEDICINE 2021: THE VIRTUAL VERDICT

Teleophthalmology wasn't a perfect solution during the pandemic, but its potential looms large, especially in large-scale screening programs.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

Telemedicine is a rapidly expanding, multifaceted field that's seeing a marked uptick in use.[1] From large-scale screening programs at research institutions to the virtual visits implemented by practices across the country in response to the pandemic, telemedicine has aided triage, reduced COVID-19 transmission,[2] saved some practices from closing and expanded care to underserved populations.[3,4] However, its usefulness in clinical practice now is limited by the technology available to clinicians and patients, and in some cases by the clinicians and patients themselves.

In this article, telemedicine experts discuss some of the ongoing work in large-scale screening programs, and clinicians share their own telemedicine experiences during and after the pandemic.

Screening Programs

"Telemedicine for diabetic retinopathy is well established, much more so than for glaucoma," says Albert S. Khouri, MD, a professor of ophthalmology and a glaucoma specialist at Rutgers New Jersey Medical School. "The form of telemedicine we've used for community screening dates back more than 15 years. The program has evolved along with the technology, and the protocols and algorithms we use have evolved as well."

Dr. Khouri says the Rutgers mobile clinic recently resumed community outreach programs, after a short pause during the pandemic (*Figure 1*). The mobile unit, which contains a portable OCT, is driven around the state to schools, soup kitchens, community centers, churches, temples and mosques. "The program is typically advertised within the local community, and then we screen subjects for vision-threatening diseases—the big four being glaucoma, macular degeneration, DR and cataracts. We identify pathology and either refer patients to a local ophthalmologist or to the university for continuity of care."

Screening patients with the mobile clinic is very efficient, says Dr. Khouri, who presented a study on the protocol's time efficiency at ARVO several years ago. "We use motorized tables that elevate the equipment and screen patients standing up," he explains. "Sitting, standing and then sitting and standing again is the most time-consuming aspect of screening, especially when dealing with elderly patients. Measuring visual acuity, IOP and obtaining anterior and posterior segment images takes about two to three minutes per subject. All the data is then transferred to a computer, and whoever is directing the operation at the time goes over the findings with the subject, or communicates with an off-site ophthalmologist, to give the patient a recommendation in real-time."

At Stanford Medicine's Byers Eye Institute, David Myung, MD, PhD, an assistant professor of ophthalmology, leads the Stanford Teleophthalmology Autonomous Testing and Universal Screening (STATUS) program. The Bay-Area-wide program uses artificial intelligence and telemedicine to detect referral-

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Albert S. Khouri, MD

Figure 1. The Rutgers' mobile clinic has been screening community members for vision-threatening diseases for more than 15 years.

warranted diabetic eye disease at Stanford Medicine-affiliated primary care clinics.

Dr. Myung says that when they began the program using tele-ophthalmology alone, they saw a consistent improvement in the ability of the primary care clinics to increase patients' adherence with annual retinal exams, an important quality-of-care measure in the management of patients with diabetes. "The program enabled the clinics to exceed their goal of hitting the 90th percentile for this measure, which is part of the Healthcare Effectiveness Data and Information Set (HEDIS), even in the midst of the pandemic. It was a great demonstration of how a telemedicine program can tangibly affect patient health on a larger scale."

Dr. Myung is also a member of the executive committee of the Collaborative Community on Ophthalmic Imaging (CCOI), a group of stakeholders—including members of the U.S. Food and Drug Administration, the National Eye Institute, leading professional societies and patient organizations—that seeks to clarify the challenges, best practices, strategies and standards for ophthalmic imaging.[5] "During our conference last September, we had a vibrant discourse on diseases that lend themselves well to the use of AI for image interpretation, such as ROP, macular degeneration, ocular oncology and glaucoma," he says. "As a community, we're considering the steps needed to bring autonomous testing and AI algorithms to critical use for these diseases. We'll be discussing these and other topics germane to ocular imaging further at our upcoming conference in January."

The autonomous AI-based testing component of the STATUS program launched in December 2020. "We've now seen seven primary sites that use IDx-DR, an FDA-cleared AI algorithm for detecting referral-warranted diabetic retinopathy," says Dr. Myung (*Figure 2*). He describes the program as an "AI-human hybrid" model where the image interpretation load is shared between the AI software and human providers at the Stanford Reading Center (STARC), which is led by his colleague, Theodore Leng, MD, FACS, an associate professor of ophthalmology. They say they've found that this model triages the more challenging images to retina specialists, helps more patients get screened, and ultimately enables patients to be referred appropriately for in-person care.

"Implementing AI into the system involved a highly collaborative effort between ophthalmologists, primary care providers, ambulatory care leadership, IT and cybersecurity, among many others," Dr. Myung says. "Now, with this AI-human hybrid workflow model in place, we're excited about what our program can do to further facilitate efficient and timely care for our patients."

Uncovering Other Pathology

Dr. Khouri and his colleagues published a clinical study in 2020 through the New Jersey Health Foundation comparing tele-glaucoma and clinical evaluation before the pandemic, that demonstrated its potential to mitigate some clinician bias when making diagnoses.[6]

"We ran patients through a tele-glaucoma virtual model and collected data, including visual acuity, IOP and anterior and posterior segment imaging, which were evaluated remotely by a reader for diagnosis, management and follow-up," he says. "In the clinic arm, patients went to a glaucoma clinic routinely as they would if they were examined at the university and got the routine standard-of-care examination, which included visual acuity, pressure, a slit lamp exam, HVF and OCT, as needed.

"We compared outcomes between the tele-glaucoma arm and the face-to-face arm, in terms of accuracy of diagnosis and treatment recommendation," he continues. "The two arms were comparable, but there were advantages and disadvantages with each. The face-to-face visit is standard of care and demonstrated superior accuracy of optic nerve head assessment and functional data acquisition. The tele-glaucoma arm

was completely lacking in HVF data, but it had the advantage of a being a quicker visit. It was significantly shorter than an office visit."

Surprisingly, his team found that ancillary non-glaucoma diagnoses were more likely in the tele-glaucoma arm. "That group underwent non-mydriatic posterior pole digital imaging," he explains. "We uncovered other pathology like hypertensive retinopathy or AMD drusen that were overlooked or not picked up as a diagnosis at the office visits, where the clinician knew the patient was coming in for glaucoma management and treated the glaucoma but didn't comment on the ancillary findings picked up by tele-glaucoma imaging." This corroborates the findings of a previously published literature review of real-time teleophthalmology and face-to-face consultation, which found that, in terms of diagnostic accuracy, teleophthalmology was superior in one study and comparable in six.[7]

Dr. Khouri says his study demonstrated that telemedicine for glaucoma is a viable option. "You can be very accurate in your diagnosis," he says. "But the study also highlighted the shortcomings of tele-glaucoma, particularly with the functional aspect, which is very important. We're not just treating pressure measurements in these patients. Functional testing—mainly peripheral vision testing or visual field testing—is paramount when discussing quality of life with these patients. That piece was missing from the telemedicine part. I'm hopeful that with all the innovation—there are some virtual reality or objective visual field tests in the works—we'll be able to improve on this."

David Myung, MD, PhD

Figure 2. The IDx-DR launch at Santa Clara. Stanford Medicine incorporates artificial intelligence in its Bay-Area-wide program for diabetic eye disease testing and screening. (From left to right, back: David Myung, MD, PhD, Marcie Levine, MD, Jill Terrill from Digital Diagnostics; front: Elizabeth Greksouk, NP.)

Telepresence Robots

While it sounds a little futuristic, telepresence is just a fancy word for synchronous telemedicine, where doctors connect with patients in real time, as they would in the office, explains Dr. Khouri. He and his students began a telepresence robot project before the pandemic, but when Rutgers' COVID restrictions prevented conventional means of research, the project really took off. "One of my students, Ashley Ooms, came up with the idea and executed it," says Dr. Khouri. "She knew we had a robot that we'd used at community screening events in Florida; she used it remotely to deliver questionnaires and teaching modules to patients to find out how much they knew about glaucoma. We hoped to enhance their understanding about glaucoma and their use of topical medications."[8]

The robot consists of an iPad-like screen and camera at the end of a pole that moves on a single wheel (*Figure 3*). A doctor can drive the robot from a smartphone, as well as raise and lower the camera and screen to be eye-level with the patient. "We can put a Snellen chart on the screen, but it's tedious to move the robot to a specific distance from the patient," notes Dr. Khouri. "We mostly used it for real-time communication with patients who continued to come in for glaucoma treatment, and for patient education, delivering questionnaires, collecting data and counseling subjects when an ophthalmologist wasn't on site.

"We didn't know what to expect when we ran the study, but we were pleasantly surprised," he continues. "The majority of patients received it very well. Instead of just hearing an ophthalmologist through the speaker of a phone, they can see you, and the level of communication and connection is much better when it's both audio and visual. The fact that you could navigate the robot around made it more realistic. The issue with it though, is cost, and the models are still a little clunky. We weren't that great at driving the robot—we'd bump into things. Driving the robot also depends on your internet bandwidth. If the Wi-Fi is spotty, it's hard to drive until the signal is stronger."

Pandemic-era Practice

"In ophthalmology we're challenged and blessed with the necessity of specialized equipment," says Brandon Baartman, MD, a cataract, cornea and glaucoma surgeon in practice at Vance Thompson Vision in Omaha, Nebraska. "When the coronavirus pandemic hit, we all had to adapt to continue caring for patients with chronic issues. Unfortunately, during the pandemic, many of these patients were still lost to follow-up, resulting in poor outcomes."[9]

In early 2020, there were more unknowns about the virus, he notes. "The medical community wasn't sure then how the virus spreads or whether it could exist on surfaces. Many of our early efforts were put in place to protect patients against some of those unknowns. At my

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practice, we used virtual visits for certain acute cases like red eye and for triage. We created a separate schedule in our practice management software with time slots for virtual visits."

Initially, many practices relied on video conferencing programs like Zoom and FaceTime to reach patients—and the relaxed regulations enabled this emergency use—but most soon switched to dedicated telehealth solutions with HIPAA-compliant software. "We tried to be adaptive to the technology constraints of our patients," says Dr. Baartman, who used Doxy.me to manage virtual visits.

"Virtual visits worked mediocrely for us at best," he continues. "There were very few problems that patients came to us with that we could confidently treat and manage with a virtual visit. We're a largely surgical referral practice, so we ended up seeing a lot of those patients in-person after a virtual triage. Our virtual visits slowed down over the course of 2020 and were almost nonexistent in our practice come early 2021, when we saw a decrease in COVID cases and an increase in the understanding of the virus and how it spreads. It also coincided with an increase in vaccination and vaccine availability.

"At our peak we probably did about three or four virtual visits in a day—it was challenging to instruct our team, when a patient called in, on who could receive a tele-visit and who needed to come in for an exam. When we reopened more routine care in mid-2020, we kept virtual slots open, but many patients began returning, just out of a need to leave the house and have some social interaction."

Dr. Baartman says his practice billed only a small percentage of virtual visits, because most of them turned into triage, "which we ultimately felt was our responsibility as providers, since we often had the patient come in anyway." He says that when his practice shut down, billing some virtual visits was better than no revenue, but with the PPP loans, ability to see patients on an emergent basis and his practice's aggressive reopening strategy, "we certainly didn't think the time it took to coordinate and deliver care virtually ended up being a financial factor for us."

Albert S. Khouri, MD

Figure 3. In a study, physicians and medical students at Rutgers University used telepresence robots to deliver patient education and perform synchronous teleophthalmology visits with patients. However, users say the robots were a bit difficult to maneuver, especially if the Wi-Fi signal was weak.

Here's how some other subspecialties fared:

• ***Glaucoma.*** Though mobile units like Rutgers' exist, that form of telemedicine is very different from most virtual visits conducted during the pandemic. "Virtual visits came about mostly during the pandemic for us," says Dr. Khouri. "COVID really catapulted telemedicine from a niche process at select sites in the country, such as the VA system and research or academic centers, to being readily available to patients almost everywhere. But we really had no access to objective data during virtual visits. The most value was in maintaining connection with patients, reinforcing medical recommendations and making sure patients had access to their medications."

When Dr. Khouri and his colleagues realized the shortcomings of virtual visits, they quickly set up a different protocol to create a hybrid virtual visit. This hybrid model, which they used during the heavy months of the pandemic, employed a drive-thru where patients could be evaluated by a small eye-care team for visual acuity with a Snellen card and IOP with both Tono-Pens (Reichert) and iCare handheld tonometers, which have disposable tips. "We were also able to perform handheld slit-lamp exams, but we couldn't image the fundus with this care model," he says. "We did virtual visits later that day."

At ARVO and AAO in 2020, his team presented a study comparing the drive-thru and virtual visit model to just a virtual visit. "In ophthalmology, with virtual visits alone, we're less likely to make any treatment-altering recommendations," he says. "With a hybrid visit, we're more likely to adjust medical treatment. There were limitations to the hybrid model, however. Patients had to drive to a separate location to get measurements. Once vaccinations picked up and things began to reopen, it didn't make sense for the patient to drive all the way to the office and not come inside for a proper slit lamp exam."

• ***Retina.*** Retina specialist Shriji Patel, MD, MBA, of the Vanderbilt Eye Institute says, "Telemedicine is far from where we want it to be; however, it was an excellent stopgap at the time when it was unsafe for patients to come into the office and be around other patients or providers."

His multispecialty practice used Epic's HIPAA-compliant telemedicine visit option. "We were able to keep it secure and safe, and patients would connect through their Vanderbilt electronic health portal so it was a seamless entryway," he says. "We'd have the telehealth visit on our templates as a scheduled visit. Patients would be queued up for us in the virtual waiting room, and then we just clicked a button to start the visit. We used it a little for patients who we absolutely needed to get a read on but couldn't come in, but I'm not convinced it was much more helpful than a phone call."

Dr. Patel says that during virtual visits, he was able to deal with triage issues and assess to some degree how an eye was doing postoperatively. "This was mainly done by gathering information from the patient: how is the eye feeling, what's your vision like? Is this superficial bleeding that's typical in a postop course, or is there blood vessel dilation and tortuosity suggesting inflammation? Are there signs of infection—a hypopyon? These were about all we could assess from a virtual visit."

Additionally, he says that getting used to the software was challenging for patients and providers. "We had to have IT support on hand to make sure everyone could sign in and get on the system at the appropriate times."

Like Dr. Patel, Ken Lord, MD, of Retina Associates of Southern Utah, didn't find telemedicine particularly useful for his subspecialty. "We limited a lot of our routine follow-ups during the height of the pandemic, and we kept seeing our injection patients, but that was about it," he says. "We never did any telehealth. If we had patients who needed to see us for emergencies, there wasn't much telehealth could do."

• ***Cornea and cataract.*** As expected, telemedicine was slightly more applicable in anterior segment subspecialties; however, the lack of objective data still hindered its utility. Josh Frenkel, MD, MPH, of Wang Vision Institute in Nashville, an anterior segment surgeon, says his practice began using telemedicine during the pandemic for cataract and refractive surgery screenings.

"We continued virtual visits with Doxy.me for a while after we opened again, and our optometrists did some as well," he says. "Patients seemed to enjoy virtual visits they could do from home. However, after a while it became challenging because virtual visits required extra time during the workday. Our clinic was busy enough that we didn't have the capacity to keep them in."

He says telemedicine has the potential to increase the number of refractive consults his practice does. "Right now, we have one of our patient coordinators, who's working remotely, follow up on leads and do LASIK consults over the phone," he notes. "That's helped workflow efficiency, and it's more convenient for patients—getting them that first touch-point for their initial evaluation. It's helped weed out non-candidates. These refractive screenings have worked best with telemedicine because the age group is largely comfortable with using digital technology. LASIK also isn't insurance-based, so we don't have to worry about coding and reimbursement for screening calls. Your refractive coordinator might be a good person to take on this role. Any way you can save doctor time is beneficial to the practice."

Dr. Myung has been implementing virtual care paradigms during the pandemic through the VA Palo Alto Health Care System. "The VA is a leader in virtual care tools," he says. "We were able to implement secure video visits very quickly during the pandemic for patients who wanted it because the telehealth infrastructure was already in place."

Prior to the pandemic, Dr. Myung piloted a remote surgical preoperative evaluation program for the VA, where preop evaluations were handled remotely prior to cataract surgery. "We found that we were able to do a lot of the preoperative management remotely so that the patients didn't need to make multiple trips to Palo Alto from far away before their operation," he says. "The proof-of-concept program worked well, with care starting with a technician-only visit for diagnostic testing and imaging, followed by a synchronous telehealth visit with an eye-care provider."

He says this work is now part of a larger effort by the VA to expand access to care across its Veterans Integrated Service Networks through the new Clinical Resource Hub (CRH) program. "Through the CRH program, we're working on ways to expand access to both medical and surgical care through the VA system to our veterans in more remote areas. For surgical specialties like ophthalmology, we're focused

on diagnosis and surgical decision-making via virtual care and providing surgical services when and where appropriate."

• ***Pediatrics.*** Ken K. Nischal, MD, FAAP, FRCOphth, the division chief of pediatric ophthalmology at Children's Hospital of Pittsburgh and medical director for digital health of the hospital, says the pandemic has been a crucial moment in American medical health delivery. "Until this public health emergency, patients had to be seen in a facility," he says. "You couldn't see them at home and be paid for it. The Medical Assistance Bulletin has said that no matter what happens after this emergency, home consultations will continue."

Dr. Nischal's hospital developed a pediatric telemedicine program in response to the pandemic. He and his colleagues published a paper detailing their implementation methodology in the *Journal of American Association for Pediatric Ophthalmology and Strabismus*.[10] The study covered outpatient records from March 21 to April 10, 2020. Before March 21, scheduled patients were categorized into three groups: requiring 1) an in-person visit, 2) a face-to-face visit that could be postponed and 3) a consultation that could be virtual.

The ophthalmology service offered the option of a virtual visit to 237 patients and scheduled 212 visits, with 25 patients declining. Those who declined a virtual visit were offered a telephone visit, and if they still declined, they were then offered an in-person visit when it was deemed safe. The ophthalmology service completed 206 (97 percent) of scheduled visits during the study period with seven providers. A total of 43 visits were with new patients, and the other 163 were follow-ups. After an initial visit, 21 patients required a virtual follow-up an average of four weeks later, and 170 required an in-person visit an average of 4.6 months later. None of the patients needed to be seen within 72 hours. Within the hospital-wide urgent care virtual platform, a total of 290 patients were seen, with 25 eye-related visits (eye pain, conjunctivitis, edema of lid(s)), and none of these patients ended up being seen at the ophthalmology clinic, but may have been followed up elsewhere.

"We posted a video on YouTube explaining how to test your child's vision before the telemedicine appointment using various apps," he says. "Many parents found it difficult to download or use the apps, however. Our ophthalmic technicians would do an intake by phone the day before the appointment and ask about any changes since the last visit. Almost all of these patients were follow-ups.

"For new patients, we created an algorithm so they could be seen safely," he continues. "In the paper, there's a list of conditions that would require a primary in-person visit (e.g., amblyopia, optic neuritis, myasthenia) or a primary telemedicine visit (e.g., chalazion or mild conjunctivitis referred by a PCP/ED in new patients; a first postop visit for lid laceration or strabismus surgery; or testing results for electrophysiology)."

During a virtual visit with video, the ophthalmologist would perform an external examination by instructing parents to position the child closer to the camera; assess extraocular movements with a fixation target; and simulate a cover test by asking parents to cover eyes alternately. They would then perform a risk/benefit analysis and triage patients into video management or an in-person visit.[10]

Dr. Nischal says telemedicine consults have helped his colleagues take weight off their in-person schedules. "All of the attendings in my division had two or three telemedicine slots during administrative time," he says. "It's easy to sit and do some administrative work and also do a few telemedicine appointments. You don't feel stressed, you're reducing your in-person visit load, and you can do telemedicine at home, if you want to. It gives you flexibility."

However, deploying the program overall was challenging. The workflows and protocols were continuously refined, so standardized scripts were used to ensure communication consistency. Additionally, testing visual acuity at home with apps meant standardization was lacking, with no way to ensure proper testing distance or calibrate devices, and results were sometimes given in nonconventional notations.[10] Examining patients without a video-enabled device was also challenging.

Despite these shortcomings, he says the virtual nature of telemedicine has helped with child attention. "Communication is better," he says. "When they're just focused on you, and you on them, in front of a screen, fifteen minutes is a long time. They get to ask you questions that they might otherwise not feel able to, thinking you're too busy to answer them during an in-person visit where there are other distractions. In fact, some children with special needs are more willing to let you look at their eyes through a screen than they are in person. They don't see it as a doctor's exam because they're sitting at home.

"We also saw a very low no-show rate due to the convenience of telemedicine," he says. The scheduled clinic e-visits had a no-show rate of 3 percent in the study. "Parents love it. It saves them time, and they don't have to take time off work." He hopes a future paradigm will include remote visual assessment facilities with sophisticated testing equipment.

Improving History-taking

Without access to most objective data, the questions you ask your patients take on even more importance. "At the time, we didn't have

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the setup to do testing remotely at other sites," Dr. Nischal says. "We needed to ask very targeted and thorough questions. The art of history-taking has become defunct, for want of a better word, because of electronic medical records. We're often so busy looking at the EMR that we aren't concentrating on asking targeted questions. We also don't get a chance to sit and talk to the patient as much as we used to."

Here are some examples of targeted questions you might ask your patient and/or their caregiver:

1. If a patient is blinking a lot, and it's a recent development, you might ask about outdoor activity (did something get into the eye?), photophobia or air conditioning in the home. Do the eyes feel dry?

2. If a patient finds it difficult to open his eyes in the morning, is he sleeping with his eyes open at night? Is a caregiver checking this? "You're not able to examine a patient for lagophthalmos remotely," Dr. Nischal notes.

3. If you suspect a patient may have glaucoma, Dr. Nischal says sometimes he enlists a caregiver's help. "I ask them to close their eyes and the patient's," he says. "I tell them, 'Feel your eyes first and then feel his. What's the difference?' You have to use that kind of surrogate testing sometimes, though it's not perfect."

4. If a patient has controlled glaucoma, you might ask, "Compared to three months ago (or since the last visit), have your eyes been watering more?" Dr. Nischal suggests. "When the patient goes outside, is she photophobic? Does she seem to be bumping into anything? When walking through doorways, is she bumping into the frame with a certain side of her body? If the patient is encountering any of these problems, I have them come in."

A Work in Progress

Telemedicine technology is evolving at an impressive speed. Yet, experts say we're still just on the cusp of what's possible. "Telemedicine was a learning experience," says Dr. Baartman. "I'm hopeful that it'll evolve into a practice-enhancer for patient accessibility purposes, but we're still waiting for the development of the necessary at-home technology to facilitate a better exam and experience for providers and patients needing virtual eye care. During the pandemic, I felt the virtual visits were a worthwhile exercise that we hadn't found a long-term use for yet."

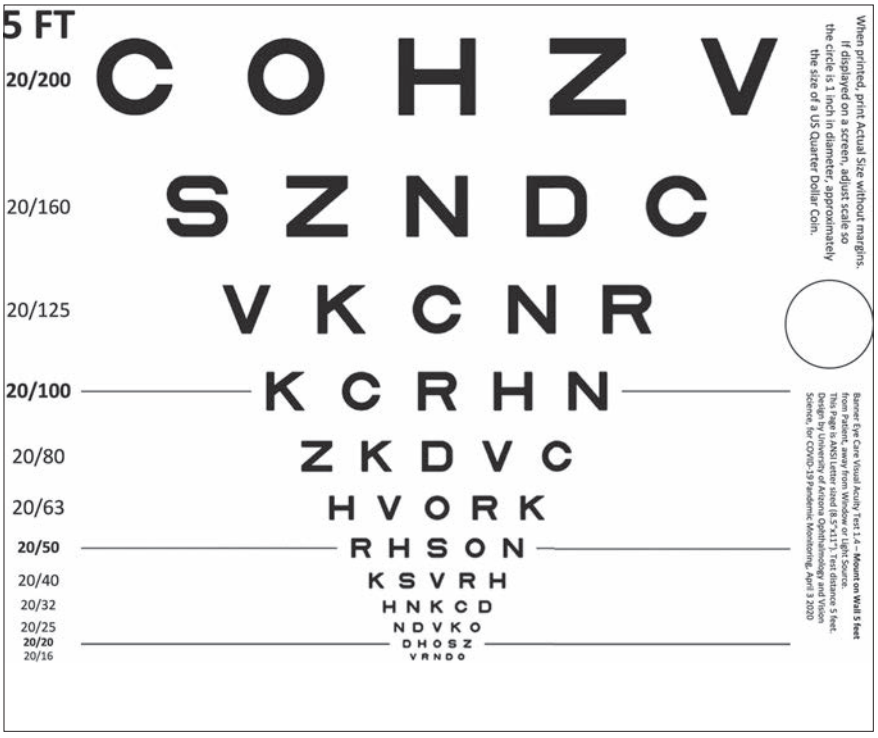

Figure 4. This printable home visual acuity test, when used with a standardized protocol, was found to produce equivalent scores to standard technician-administered tests in a study published in *Ophthalmology Science* this year.[11]

"Right now, the main goal of telehealth and remote vision monitoring is to catch disease that needs to be treated as early as possible," says Dr. Lord. He says remote vision screening and monitoring platforms for teleophthalmology will need both clinical validation and FDA approval.

There are a few already approved by the FDA, including two autonomous artificial-intelligence algorithms: IDx-DR (Digital Diagnostics) and EyeArt (Eyenuk) for detecting diabetic eye disease (see the November 2021 issue of *Review*); ForeseeHome (NotalVision), an at-home nAMD monitoring device and program; and Alleye (Oculocare Medical), a free mobile app for self-monitoring AMD progression. Needless to say, it's important to caution patients against using apps for vision testing that haven't been rigorously vetted and approved.

Here are just a few other issues that telemedicine and its users will need to address:

• ***The patient's ability to use the technology correctly.*** "In the office, we control the exam, but with at-home monitoring, the patient is in control," says Dr. Lord. "Most of our patients are over 70 and aren't as adept at handling a mobile or digital interface as younger patients. We also need to be able to get a reliable interpretation of the results they give us."

A new printable home visual acu-

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Apellis

ity test for teleophthalmology was recently validated in a study published in *Ophthalmology Science* this year.[11] The study included 209 eyes from 108 patients who had scheduled in-person outpatient clinic visits. Patients were sent a .pdf document with instructions and a printable ETDRS vision chart calibrated for use at five feet (*Figure 4*). The patients completed the test at home (with 98 percent reporting good ease of use); they were then measured by a technician using a standard ETDRS chart in the office. Mean adjusted VA letter score difference was 4.1 letters (90% CI, 3.2 to 4.9), which was well within the seven-letter equivalence margin, the researchers said. Average unadjusted VA scores in clinic were 3.9 letters more than scores at home (90% CI, 3.1 to 4.7), and absolute difference was 5.2 letters (90% CI, 4.6. to 5.9). The researchers said the standardized-protocol at-home test was equivalent to a standard technician-administered test in the study.

• ***The clinician's ability to stay on top of compliance.*** "It's a big responsibility to manage the health of a patient remotely," Dr. Lord says. "There are a lot of compliance issues you need to be aware of, especially when it comes to managing patient data." Be aware of licensure, state regulations, synchronous versus asynchronous visits, patient consent for telemedicine, parity laws, Medicare restrictions and HIPAA.[12]

• ***Data privacy.*** Any device or telehealth platform that's gathering patient information must be HIPAA compliant, but it's difficult to ensure this. Physicians should be careful about the service they choose. "This has to be a priority for developers," says Dr. Lord. "Patients' information must be private, and the servers and anything else gathering patient data must also be secure and HIPAA-compliant. The other option is to not gather data, and to have the device simply tell the patient, 'yes, you're fine' or 'no, you're not,' and leave it up to the patient to contact a provider if they're not doing well."

Before the device meets the home user, developers and regulatory bodies will also need to consider questions of data privacy for the algorithms, which need large datasets to train on. Removal of identifiable information from large datasets is difficult, and reidentification may always be a concern.[13]

• ***Establishing standards.*** Standards for image acquisition, image and data transfer, interpretation and encryption are all needed. "With DR, many years ago we established standards for DICOM transmission of images and how you interpret pathology for DR on a standard image," notes Dr. Khouri. "Other diseases like glaucoma are really on a spectrum, so we don't have standards for acquisition, transmission and interpretation of data."

• ***Ensuring equity.*** Screening programs, in particular, have great potential in underserved communities, but screening is only one part of teleophthalmology. Virtual visits depend heavily on individuals' access to digital technology, such as computers or smartphones with good-quality cameras, internet access and tech literacy. If the pandemic has showed us anything with regard to healthcare access and remote schooling, it's that not everyone has these. Black and Hispanic people are more likely to suffer from visual impairment and be less digitally literate, while being less likely own a smartphone or have access to quality internet.[14]

Dr. Nischal says video visits have been advantageous since they enable you to take a screenshot of the patient's eye as you conduct the exam, but the quality of the image is heavily affected by the patient's internet bandwidth. "The less well-off you are, the more likely it is that you'll rely on cellular data, rather than a true Wi-Fi router in the home," he says. "The quality of what you see over cellular data isn't as good as high-bandwidth Wi-Fi. We may be improving access, but the quality of what you access isn't equal."

• ***Counseling patients carefully about self-monitoring.*** With more at-home monitoring technology in development, it'll be important for doctors to not only instruct patients on how to perform the tests, but also to counsel them about what they may find. For example, some patients use home tonometers to report their pressures, which has the benefit of obtaining IOP at several times a day, as opposed to during a single office visit. However, Dr. Baartman says he's seen patients go over the top checking their pressures. "They become concerned with what could otherwise be a normal fluctuation in eye pressure," he says. "Putting more technology in patients' hands is definitely a double-edged sword. They may become too fixated on their disease."

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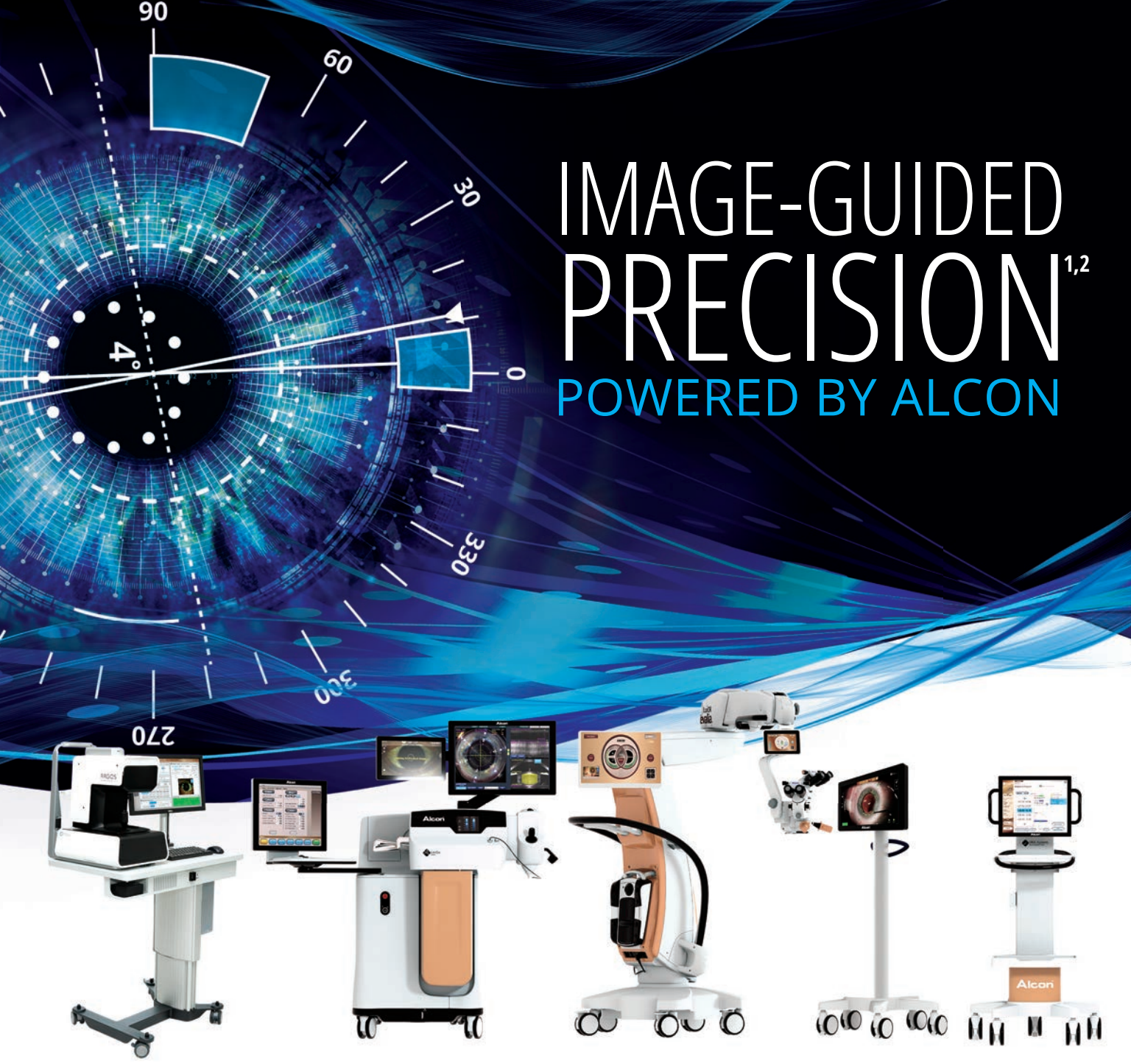

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FACILITATING PHACO WITH CUTTING-EDGE TECH

Today's machines for emulsifying and removing cataracts while managing the anterior chamber are the best ever when it comes to safety, efficiency and ease of use.

CHRISTOPHER KENT
SENIOR EDITOR

Today, cataract surgery—the most performed surgery in the world—is a very high-tech operation. Because today's surgeons use some of the most sophisticated tools available in medicine, understanding the technology has become as important as understanding how to perform the surgery itself.

"Phacoemulsification is a very complex, delicate surgery," notes Nick Mamalis, MD, a professor of ophthalmology, director of ocular pathology and co-director of the Intermountain Ocular Research Center at the Moran Eye Center at the University of Utah in Salt Lake City. "You can get into trouble if you don't do it properly, or if you don't have the proper equipment. But all of the phaco machines have gotten much better in recent years. That makes a big difference—especially with novice surgeons.

"My colleague, Randy Olson, MD, has been doing a series of experiments looking at the effectiveness of this new generation of phaco technology," he continues. "His team has found a way to modify a pig's eye nucleus to mimic the characteristics of a human nucleus. Then he sees how efficiently the new technologies emulsify little cubes of that nucleus material. Each of these systems has been shown in the lab to efficiently dissect a hard-lens nucleus without using much energy inside the eye. This is a big advance in phaco, across the board."

Here, surgeons share their experience with three of the most advanced phacoemulsification machines currently available in the United States (in alphabetical order): The Centurion (from Alcon); the Stellaris (from Bausch+Lomb); and the new Veritas (from Johnson & Johnson Vision). Then, they offer some tips for making the most of whichever machine you're using.

The Centurion

Alcon's Centurion features Active Fluidics, a system that compensates for pressure changes in the eye during surgery, thus helping to maintain a surgeon-selected IOP. The company says the combination of Ozil Technology (relating to the phaco tip's motion), the Intrepid balanced tip and the Centurion's fluidics allows for enhanced emulsification that requires minimal fluid and produces a reduced temperature rise inside the eye. (The company says the cumulative dissipated energy generated during surgery is 39 percent of that generated by the previous Infiniti Vision System.)

According to Alcon, additional key features of the Centurion include:

- a graphical user interface that displays essential data and allows the surgeon to easily adjust system parameters;
- a wireless remote that allows technicians to control the machine from different areas within the OR;
- an HD monitor with a 19-inch adjustable touch-screen interface that's easily visible;
- an adjustable instrument tray for ease of working on either eye;
- a task light for illumination wherever it's needed;
- a foot handle that allows sur-

This article has no commercial sponsorship.

Dr. Garg is a consultant to Johnson and Johnson Vision. **Dr. Rowen** consults for Alcon and Bausch + Lomb. **Dr. Yeu** consults for Johnson & Johnson Vision and is on the speaker's bureau for Alcon. **Dr. Mackool** is a consultant for Alcon. **Drs. Dhaliwal, Hardten, Mammalis** and **Hansen** report no financial ties to any product discussed.

geons and techs to move the machine after scrubbing in;

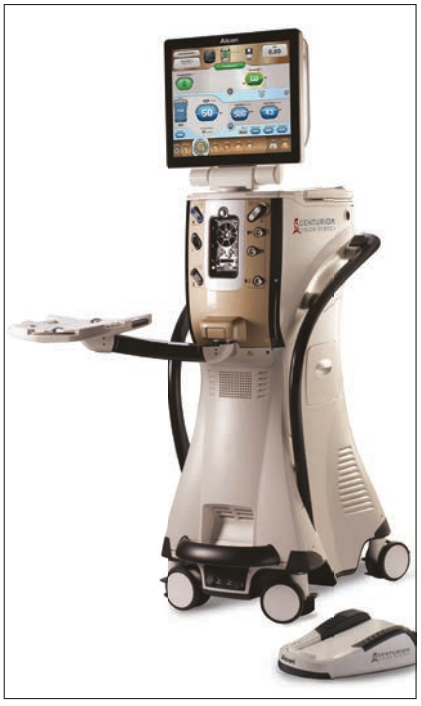
• an ergonomic, easily storable wireless footswitch that allows extended mobility in the OR, with an optional power cord for additional power.

Conquering the Surge

Dr. Mamalis says his phaco experience has largely been using the Centurion. "This machine has been quite an advance," he says. "When we're doing phacoemulsification, the ultrasound tip often catches a piece of the nucleus, and as we're trying to emulsify it, it may break loose, resulting in a post-occlusion surge and shallowing of the anterior chamber. This has long been a potential source of trouble during cataract surgery.

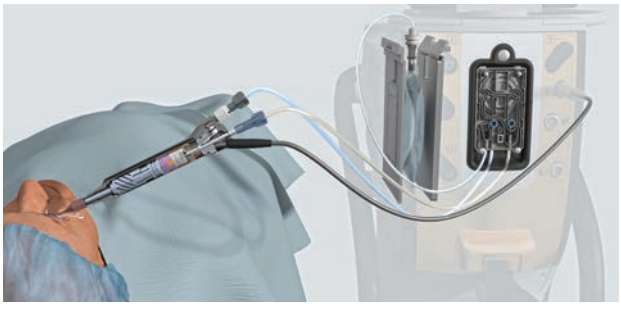
"The Centurion has a system called Active Fluidics that reduces the occlusion-break surge," he continues. "When you're preparing for surgery, you set the pressure that you want to maintain inside the eye, and the machine constantly monitors the pressure during surgery. When you get an occlusion break, the system recognizes it immediately and pumps more fluid into the system to counteract the potential surge before the chamber can shallow. I think this has been a real advance in phaco safety. Because I'm at a university, I spend a lot of time teaching residents, and they frequently get occlusion breaks. With the older systems, the anterior chamber would shallow and there'd be an increased risk of a complication such as a posterior capsule tear. That's no longer an issue."

Other surgeons agree that the Centurion's fluidics are a big selling point. Richard Mackool, MD, medical director at The Mackool Eye Institute and Laser Center, and senior attending surgeon at the Mt. Sinai New York Eye and Ear Infirmary and New York University Medical Center, believes the most important aspect of phaco technology is the fluidics. "The pressurized infusion system of the Alcon Centurion—Active Sentry—detects and responds to aspiration pressure changes within the phaco handpiece," he says.



Alcon's Centurion offers Active Fluidics for anterior chamber stability and Ozil tip movement for enhanced emulsification.

Elizabeth Yeu, MD, who practices at Virginia Eye Consultants in Norfolk, serves as an assistant professor in the department of ophthalmology at Eastern Virginia Medical School and is medical director of the Virginia Surgery Center, has used both the Centurion and brand new Veritas machines. "The Centurion has extremely stable fluidics and excellent utilization of ultrasound energy," she says. "It allows me to efficiently disassemble all densities of nuclei and trust that there will be minimal post-occlusion surge."



Centurion's Active Sentry handpiece and Active Fluidics system.

Other Features

Additional Centurion features noted by surgeons include the Ozil technology, the optional Intrepid Transformer handpiece and its ability to easily break up hard pieces of nucleus.

"With Alcon's Ozil technology, the phaco tip works with an oscillating, side-to-side motion," explains Dr. Mamalis. "The old phaco machines moved the needle in and out, almost like a jackhammer. The harder the nucleus was, the more likely it would be repulsed from the tip, leaving hard fragments bouncing around inside the anterior chamber. The Ozil system's oscillating motion allows us to keep a piece of hard nucleus at the tip, so it can be emulsified without being repulsed."

Dr. Mamalis notes that the oscillating motion also allows a hard nucleus to be emulsified more efficiently. "That means less cumulative dispersed energy, or CDE," he says. "That's important because theoretically, reducing the energy put into the eye reduces the risk of complications. In fact, this is a focus of all of the modern phaco machines: more efficient removal of the cataract without putting so much energy into the eye."

Sheri Rowen, MD, medical director at NVision Eye Centers in Newport Beach, California, and a clinical assistant professor of ophthalmology at the University of Maryland, has used both the Stellaris and the Centurion. She says she likes the Centurion a lot. "It works well, and it's very safe," she notes. "I love the way the Ozil tip works. It's very efficient. It's good at breaking up hard lenses and pulling the pieces into the port; it crushes them easily."

Deepinder K. Dhaliwal,

The Centurion's Intrepid Transformer handpiece easily converts from coaxial use to bimanual, allowing the surgeon to reach cortex directly beneath the incision.

MD, L.Ac, a professor of ophthalmology at the University of Pittsburgh School of Medicine, and the director of refractive surgery and the Cornea Service at the UPMC Eye Center, uses both the Stellaris and Centurion phaco machines when doing surgery at different locations. She sees advantages to both. "The Centurion is a great machine," she says. "It's extremely efficient when you're removing the nucleus—it rapidly emulsifies it. However, it works differently from the Stellaris. It doesn't have active vacuum. You have to occlude the tip to build vacuum."

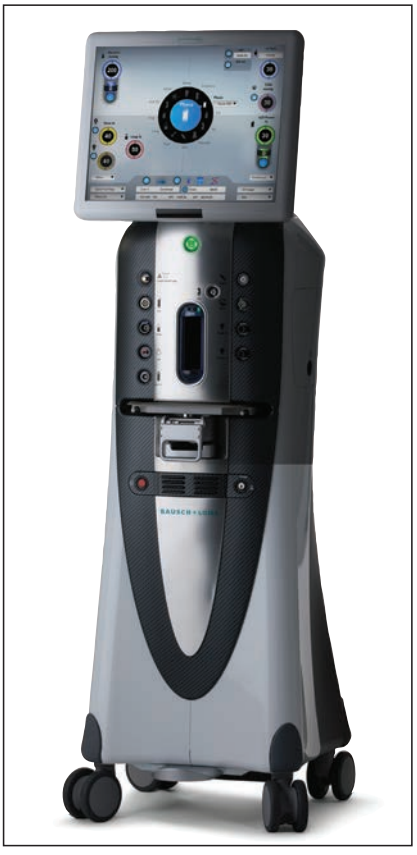
Mark Hansen, MD, anterior segment surgeon and partner at Minnesota Eye Consultants, and fellowship director and adjunct faculty member at the University of Minnesota, has used all of the phaco platforms. "One thing that's nice about the Centurion is that it has an optional irrigation/aspiration handpiece, called the Intrepid Transformer, which can be easily converted from coaxial to bimanual," he notes. "Oftentimes, the most difficult part of cortex removal is removing the cortex that's lying right below the incision. The Transformer handpiece makes it very easy to reach that because the aspiration port can be separated, allowing the surgeon to switch to bimanual surgery and use the paracentesis rather than the main incision. You just have to make an extra paracentesis, and then it's really easy to get to the subincisional cortex."

The Stellaris

According to Bausch+Lomb, the Stellaris Vision Enhancement System enables micro-incision (less than 2 mm) cataract surgery (MICS) through a flexible, hybrid approach to fluidics and advanced, ultra-efficient cutting dynamics. The company notes that the potential advantages of 1.8-mm-incision MICS include increased wound sealability; a reduction in endothelial cell loss; less surgically-induced astigmatism; and a more rapid visual recovery.

The system features:

- StableChamber Fluidics, which can be customized based on either flow or vacuum control, which the company says allows safe, efficient and predictable chamber stability during the procedure;



The Stellaris includes customizable fluidics control and a Venturi pump, the ability to perform micro-incision cataract surgery and dual-linear foot pedal control.

- the Attune Energy Management System, designed to deliver enhanced followability, reduced heat generation and increased phaco efficiency using minimal energy during cataract removal. It includes a six-crystal handpiece that delivers consistent 28.5-kHz energy with increased stroke length, and software that provides dual-linear control, front or back loading profile and programmable waveform modulation.

The Stellaris also features:

- a Bluetooth foot pedal;
- an 18-inch user interface with a video inlay and overlay; and
- a dual light source with surgeon-selected color filters that can enhance the surgeon's ability to see ocular tissue better under various conditions.

One feature that particularly appeals to many surgeons is the Stellaris' Venturi pump. "When you're performing phacoemulsification, you want safety, control and efficiency," Dr. Dhaliwal notes. "The Stellaris' Venturi pump and active vacuum give me a lot of control. I can do more specialized things when I'm using active vacuum. I can finesse things a little more."

Dr. Hansen agrees. "I like the Venturi pump system," he says. "I like the machine being reactive, moving quickly and responding to the foot pedal touch immediately, rather than waiting for the pump system to build up."

Dr. Rowen also says her favorite feature of the Stellaris is the Venturi pump. "I don't have to occlude my port to pull a piece of nucleus to it," she explains. "It's very efficient."

Additional Features

Other features that have impressed surgeons using the Stellaris include its dual-linear foot pedal, its customizability, not having to change the phaco tip, and its irrigation/aspiration handpiece tip.

"I love the foot pedal, which gives me dual-linear control of different parameters," Dr. Dhaliwal says. "I

"I was only seeing light flashes early on, but light FLASHES when you've not seen anything for so many years—it was wonderful"

—Keith H, retinal prosthesis recipient

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The Stellaris dual-linear foot pedal works well with the Venturi pump, according to surgeons. Surgeons also report that their preferred phaco tip works well regardless of cataract density.

can get just a tiny bit of phaco when I want it, especially when I'm doing epinuclear removal. I don't have to press all the way down on the pedal and build a lot of vacuum, and only then initiate phaco. That's what happens with a peristaltic machine. With a Venturi machine you can go down as much as you want on the vacuum and then just yaw over with the foot pedal and get a little bit of phaco. And, this is true in all of the different modes. When I'm sculpting, if I want a little more vacuum I can achieve that with a yaw. I feel like I have more control when I'm using the Venturi system and the dual-linear foot pedal."

Dr. Hansen also appreciates the dual-linear control provided by the foot pedal. "I find this very helpful with complex lens exchanges when a vitrectomy is planned," he explains. "Being able to toggle between irrigation/aspiration and cut is essential. Because of this ability to control the settings with the foot pedal I use the Stellaris in complex cases such lens exchanges, traumatic cataracts, dislocated lenses, and cases where I know I'm going to be doing an anterior vitrectomy."

"The Stellaris is totally customizable," Dr. Dhaliwal adds. "You can program the machine to do what you want it to do. In fact, you really need your company rep to be there when you set it up, to help you understand how the parameters should be set to work with your technique. This is definitely not 'One size fits all.' "

Another factor noted by Stellaris surgeons is not needing to change the phaco tip to manage different types of cataracts. Dr. Dhaliwal says the curved phaco tip on the Stellaris works equally well in multiple situations. "I don't switch to a different tip, whether the cataract is dense or soft," she says. "With other systems, I have to change the phaco needle to make sure I get enough cutting.

"The other thing I really like is the I/A handpiece tip, which is called 'Capsule-guard,' "she adds. "It has that name for a reason. The tip is made of a silicone that's gentle enough that it won't pop through the capsule, but strong enough that if you need to get rid of a piece of nucleus you missed, you can mash it into the I/A tip using a second instrument. You can use this tip with any phaco machine, although it's a Bausch + Lomb product."

Dr. Rowen agrees that the B+L irrigation/aspiration handpiece tip is a big plus. "The tip with the capsule guard is my favorite instrument for this purpose," she says. "It takes the cortex really nicely, and it's very safe."

The Veritas

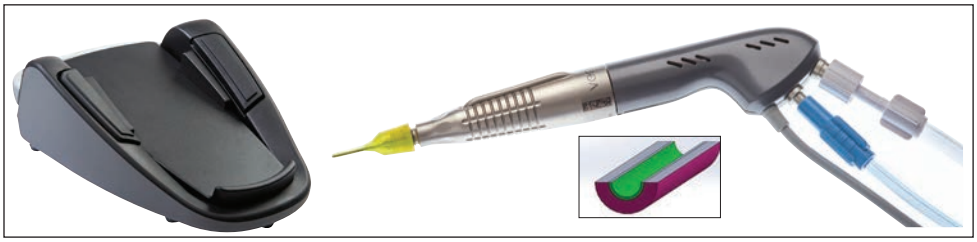
As of this past summer, Johnson & Johnson Vision announced the worldwide availability of its new Veritas Vision System. The company states that the Veritas was designed to increase efficiency, patient safety and surgeon comfort during use. According to the company, the Veritas' innovations include:

- Hybrid Fluidics Technology, designed to minimize post-occlusion surge, using Intelligent Occlusion Sensing Technologies, a system that automatically responds to occlusions.
- A phaco tip that takes advantage of the company's WhiteStar micropulse technology, featuring elliptical tip movement and using less energy than previous systems.
- Veritas' Dual Pump System, which gives the surgeon access to both peristaltic and Venturi pumps. The company says the system can transition between the two at any point during surgery, on demand.
- An ergonomically designed, comfortable-to-use foot pedal that gives the surgeon total control.

Sumit (Sam) Garg, MD, vice chair of clinical ophthalmology, medical director and a professor of cataract, corneal and refractive surgery at the Gavin Herbert Eye Institute, University of California, Irvine, has been using the new Veritas system for the past several months. He lists a number of things that he believes make the Veritas exceptional.

"Perhaps most impressive, you

The new Veritas Vision System from Johnson & Johnson Vision lets surgeons switch between Venturi and peristaltic pumps, even during a single case.



Notable features of the new Veritas machine include the ergonomic foot pedal, the swivel handpiece that reduces drag, the ability to use multiple tips and still have the system's unique elliptical tip movement, and the two-layered tubing that adds chamber stability.

can use either a peristaltic or Venturi pump—and you can use both in the same case," he says. "I typically start off making my chops in peristaltic; then I move to Venturi for nuclear fragment and viscoelastic removal. Venturi tends to be a little more efficient; with peristaltic, you get a little bit better holding of the lens when you're trying to chop it up. Maybe that flexibility doesn't make much difference in routine cases, but in complex cases it's nice to have. Also, if you're in a center with multiple surgeons who have different operating styles, this is a big advantage."

Dr. Yeu has also had the opportunity to use the new Veritas, and says her experience has been good. "The fluidics have superior stability," she notes. "The Veritas offers both peristaltic and Venturi fluidics, and I prefer to use both types. I specifically love that I can have Venturi occlusion-independent rise of vacuum during the removal of cortex, and then thorough removal of viscoelastic device after IOL placement."

Additional Features

"One key thing about the Veritas is that it lets you operate the way you want," Dr. Garg says. "It allows surgeons to customize the machine to match the way they prefer to operate. You can use a curved tip or a straight tip. You can use a 20-gauge needle or a 19- or 21-gauge needle. You can use a high-infusion sleeve.

"The company has made two changes that add to anterior chamber stability," he continues. "The system now has pressurized infusion, and a new type of tubing called dual durometer aspiration tubing. Most other tubing is made of the same material all the way through; this tubing is made from two different compounds with different rigidity. There's a slightly harder tubing on the inside, so there's less chance the tubing will collapse, and a slightly softer material on the outside, which allows for good flexibility without a lot of drag. This modification, along with the pressurized infusion, contributes to a very stable anterior chamber. In fact, because of the tubing, the anterior chamber stability is now so good that I rarely need to use the pressurized infusion.

"A third factor that's worth mentioning is that because the system is brand new, all the electronics are current," he says. "The processing speed is very fast. If you look at the bench testing done by the company, the occurrence of surge is very low and recovery is faster than any other system on the market. That has implications for patient safety."

Dr. Garg says another very useful feature only available in the Veritas is a swivel handpiece. "When phacoing you often feel a little bit of resistance or drag on the handpiece," he explains. "That's either because of the weight of the handpiece or because of the tubing. The Veritas has a swivel handpiece, where the back end of the handpiece stays fixed while the front part swivels independently. This gives you more maneuverability. I don't feel any resistance when I'm using it."

In terms of the phaco tip, Dr. Garg notes that the idea of a moving tip was invented by Alcon, currently available in their Ozil format. "The Veritas has a different movement call Ellipse, which is basically an elliptical motion," he explains. "The nice thing about it is that you can use it with any needle configuration you want, such as curved or straight. My partner uses a straight tip; I like to use a curved, beveled tip, which allows for better power modulation and more efficiency. Other machines only produce their motion with one type of phaco tip."

Dr. Garg adds that he also finds the new graphical user interface and foot pedal to be very user-friendly. "The GUI is more intuitive than the previous system [the Signature Pro]," he says. "The screen is color-coded in such a way that you can just glance at it and know exactly where you are in the system. Meanwhile, the new foot pedal is very ergonomic. I think it's an improvement over the previous version, in respect to its weight, travelability and features."

Dr. Garg says that, overall, he's found the Veritas to be very efficient. "I haven't had any issues with soft or hard cataracts, pseudoexfoliation, post-vitrectomy eyes—all of the complex cases we commonly see. So far, the machine has done really well.

"Whenever there's a new phaco machine, people want to know whether it's worth looking at, worth trying a demo," he adds. "In this case, I think it's worthwhile. It's a noticeable change from the prior version, the Signature. I didn't think the change from Signature to Signature Pro was all that dramatic. But this system is a significant advance."

Maximizing Your Machine

Whatever phaco system you're using, surgeons offer these tips to make the most of the technology:

• ***Choose a phaco machine that works best with your preferred style***

PHACO AND FEMTO

Today, some surgeons use a femtosecond laser to break up the nucleus before removal. They note that the most significant phaco machine feature in this situation is the type of vacuum it allows you to use.

"There's an advantage to using a Venturi pump if you're using a femtosecond laser to break the nucleus up into tiny pieces," notes Sumit (Sam) Garg, MD, medical director and a professor of cataract, corneal and refractive surgery at the Gavin Herbert Eye Institute, University of California, Irvine. "A peristaltic pump only builds vacuum when the tip is occluded, so a nucleus fragment will only come to the tip if it's very close. With the Venturi pump, you don't need occlusion to create vacuum. As a result, you don't need to chase the chips that are farther from the phaco tip; they come to the tip. That allows surgeons to keep the phaco needle in the center of the eye, away from delicate structures such as the iris or the posterior capsule."

Sheri Rowen, MD, medical director at NVision Eye Centers in Newport Beach, California, and a clinical assistant professor of ophthalmology at the University of Maryland, agrees. "Having a Venturi pump is ideal when you're using a femtosecond to break up the nucleus," she says. "The pieces come right up to the phaco tip."

—CK

of lens removal. Dr. Rowen points out that different phaco machine features may make more sense with a particular lens removal technique. "Some surgeons divide and conquer the lens; some split the lens; some people chop it; some hold it while they're fracturing it," she explains. "The different pumps, phaco tips and other features may be more helpful with one method of lens removal than another. Surgeons should try out the different options and pick the machine that works best with their favorite style of lens removal."

• ***Understand how your machine works before you use it.*** "Before you start using any phaco machine, it's imperative to become well-versed in its features—especially the vacuum pump—and how the machine works," says Dr. Dhaliwal. "I use both peristaltic and Venturi machines, so I know how different they are. For example, you may have to modify your technique depending on whether you have active vacuum or not. Saying that there was a problem during surgery because you didn't know how to use the machine isn't acceptable."

• ***If you switch machines, make sure your phaco tip and sleeve match your incision size.*** Many surgeons use different phaco machines at different ASCs or hospitals. "When switching to a different machine, if you're using the wrong blade for the wrong tip and the wrong phaco sleeve, you'll get a lot of leakage around the tip and cause the chamber to collapse frequently," Dr. Hansen points out.

• ***Optimize the settings to match your preferred technique for nucleus removal.*** "There are many ways to remove a cataract," Dr. Hansen points out. "You may like divide-and-conquer, or horizontal or vertical chop, or just flipping the nucleus into the anterior chamber. However, they all require different phacodynamics, so the settings should be adjusted—especially when you're starting on a new machine or switching between machines."

• ***Use your company reps as a resource.*** "Anytime you gain access to a new machine, it's extremely helpful to have the company representative give you a tour of the options, until you've fine-tuned your process to match your machine," notes David R. Hardten, MD, FACS, a founding partner at Minnesota Eye Consultants in Bloomington, Minnesota.

Technique Tips

These suggestions will help ensure that you and your phaco unit produce great outcomes:

• ***Don't limit yourself to a single phaco technique.*** "It's important to be comfortable with a wide range of techniques, so you can match the lens you're conquering," says Dr. Hardten. "Some lenses are easier to manage with a supracapsular approach, some with vertical chop, some with horizontal chop, and some with divide-and-conquer."

• ***Remember that different needles, sleeves and incisions require different phaco settings.*** "It's important to understand that changing one factor in your phaco setup will probably require a change in your settings," notes Dr. Garg. "I use different settings for different needles, depending on the density of the lens and what I'm trying to achieve. I've seen other surgeons try to use my phaco settings with a different needle, and the machine behaves differently, affecting chamber stability."

• ***Make sure the infusion is off before coming out of the eye.*** "Many surgeons leave the infusion on when they're coming out of the eye," notes Dr. Garg. "That leads to a greater chance of iris prolapse. That's especially problematic in patients who have floppy iris syndrome."

• ***If you need to perform a vitrectomy, use a smaller-bore, higher-cut-rate vitrector.*** "The newer phaco machines have very-high-cut-rate vitrectors, which is great for elective cases, or unplanned situations in which you have to do a vitrectomy," notes Dr. Garg. "The higher the cut rate, the more efficiently and safely you can remove vitreous, without causing traction. All of the new systems offer this, but many surgeons will stick to a larger-bore, 20-gauge vitrector. Having that much vitreous sucked out at once can be quite jarring to the eye. Using the smaller bore allows for a smoother removal of vitreous, whether planned or unplanned."

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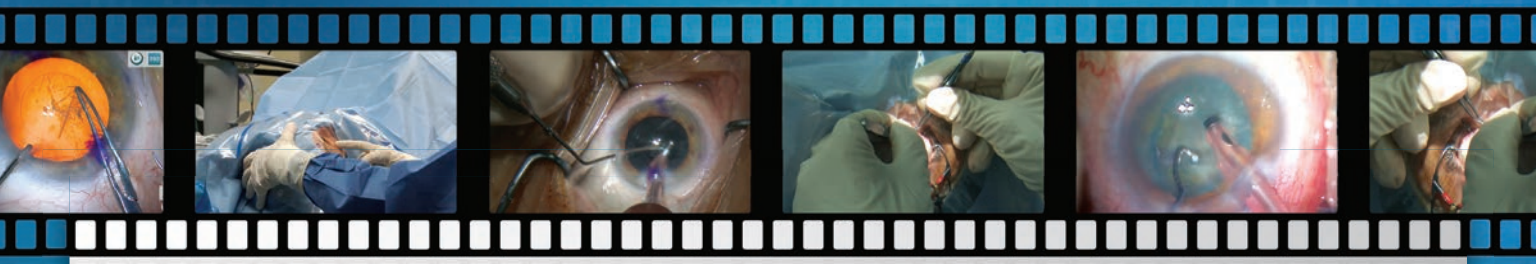

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RVO: Diagnosis and Management

A comprehensive look at occlusions' etiology, risk factors, signs, symptoms and treatment.

KATHERINE TALCOTT, MD
CLEVELAND

Retinal vein occlusions are a common but heterogenous group of retinal disorders characterized by impaired venous return of the retinal circulation. Though RVOs share common clinical features, they're distinct entities with their own risk factors, prognosis and—sometimes—treatments. There's also a wide spectrum of clinical severity of RVO and, if left untreated, RVO can lead to permanent vision impairment. Early recognition and prompt treatment, if needed, are key to preserving vision. Here, I'll outline the features of the different kinds of vein occlusions, the best way to diagnose them and the most effective course of treatment.

Classifying Occlusions

Classification of RVO can be divided into branch retinal vein occlusion, hemiretinal vein occlusion and central retinal vein occlusion, depending on the location of the obstruction. If the occlusion occurs within or posterior to the optic nerve head (often a thrombus in the central retinal vein near the lamina cribrosa), it's termed a CRVO. If the occlusion is at the major bifurcation of the central retinal vein, it's an HRVO, and any obstruction within a tributary vein (often a thrombus at the arteriovenous crossing point) is a BRVO. Often, HRVO is a considered a separate condition that can behave in a way that's between a BRVO and CRVO.[1,2]

Epidemiology and Risk Factors

Together, RVOs represent the second leading cause of retinal vascular blindness after diabetic retinopathy. BRVO is more common than CRVO.[3-6] Worldwide prevalence of BRVO is estimated to be 0.4 percent, and CRVO around 0.08 percent, with a symmetrical distribution between men and women and increased risk with older age.[7] In the Beaver Dam Eye Study, at 15 years the cumulative incidence of BRVO was 1.8 percent, vs. 0.5 percent for CRVO.[8] The Blue Mountain Eye Study showed a 0.7-percent incidence in patients younger than 60 years, increasing to 4.6 percent in patients 80 years and older.[5]

The greatest predictor of developing RVO is an RVO in the contralateral eye. Individuals with BRVO in one eye have a 10-percent risk of any RVO in the contralateral eye within three years.[9] The estimated risk of contralateral involvement in a patient with CRVO is approximately 1 percent per year, but increases to 7 percent at five years.[9,10]

RVOs have been associated with certain systemic vascular risk factors, including hypertension, hyperlipidemia, diabetes, active smoking and peripheral vascular disease.[3-5,11,12] Of these systemic risk factors, one meta-analysis found that 47.9 percent of RVO cases were attributed to hypertension, 20.1 percent to hyperlipidemia and 4.9 percent

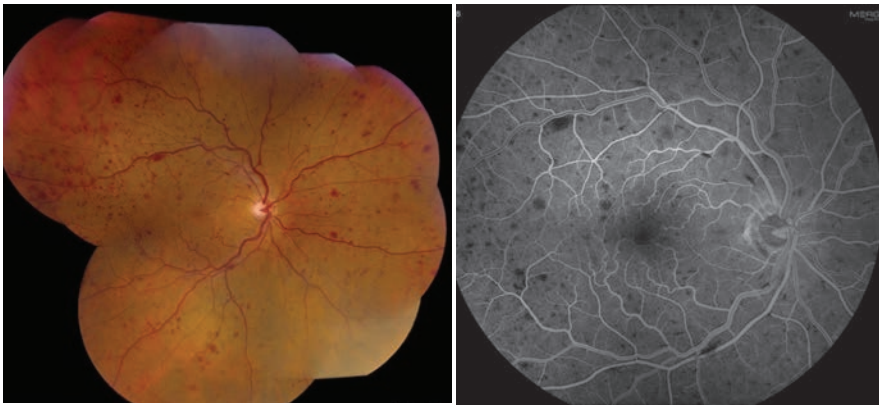

Figure 1. Fundus photograph and fluorescein angiogram of a non-ischemic central retinal vein occlusion.

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.

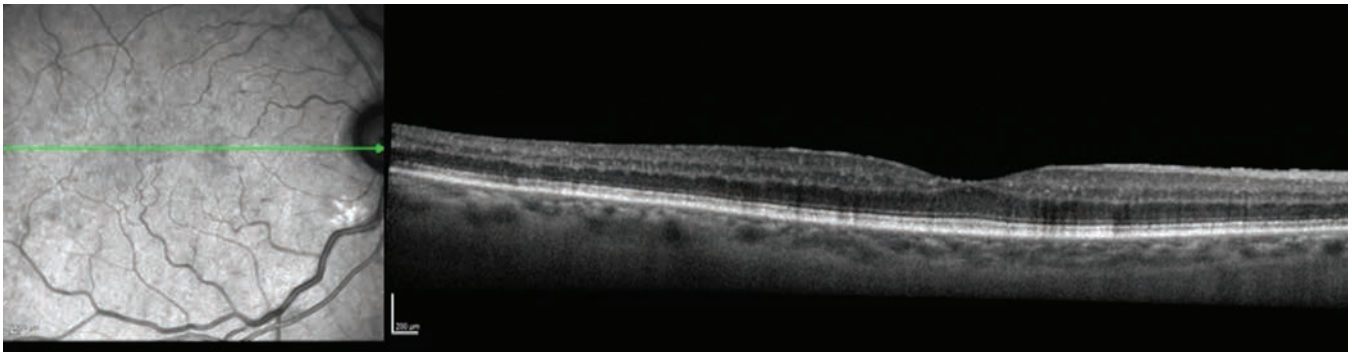

Figure 2. Optical coherence topography of the patient from Figure 1 didn't show any significant macular edema.

to diabetes.[13] The study concluded that hypertension and hyperlipidemia were common risk factors for all forms of RVO in adults, whereas diabetes was less significant due to its inconsistent association with BRVO. Some studies have shown an increased risk of cerebrovascular and cardiovascular disease in patients with RVO, including a greater risk of developing acute myocardial infarction after a diagnosis of RVO, although other studies have shown similar rates of stroke and myocardial infarction.[14-17]

There is some controversy surrounding hypercoagulable states and RVO. One meta-analysis of 26 studies found that thrombophilic risk factors, hyperhomocysteinemia and anticardiolipin antibodies were significantly independently associated with RVO.[18] Other associations include proteins C and S deficiency, high alpha-2 globulin concentrations, higher activated factor VII concentrations, oral contraception use and increased blood viscosity.[12,19]

Additionally, open-angle glaucoma is a common ocular comorbidity in RVO patients.[11,20] Glaucoma, along with sleep apnea, is more common in CRVO than BRVO.[21,22]

Clinical Features

RVO patients are at risk of vision loss from several complications of the interrupted blood flow, including macular edema, macular ischemia, optic neuropathy, vitreous hemorrhage and tractional retinal detachment. However, symptoms related to an RVO can be subtle, especially if the severity is mild or the impacted area is outside the macula. Acute RVO commonly presents with painless visual disturbances. Visual field abnormalities can be present but are rarely symptomatic.[23] Increased intravenous pressure can result in vascular tortuosity, retinal hemorrhages (superficial flame-shaped and deep blot), cotton wool spots and optic nerve edema. RVO can be classified by anatomic location. BRVO occurs in one retinal quadrant and can be distinguished by hemorrhage in that area. HRVO patients show findings only in the impacted hemifield, while CRVO patients can show retinal hemorrhages in all four quadrants. Congestion of the capillary bed can lead to macular edema, metamorphopsia and decreased visual acuity. Severe congestion can also result in vitreous hemorrhage, which can be difficult to distinguish from vitreous hemorrhage related to ocular neovascularization.

BRVO typically occurs at arteriovenous crossings where the artery and vein share an adventitial sheath. The artery has been observed to cross the vein anteriorly in 98 to 99 percent of BRVO, compared with approximately 60 to 70 percent of unaffected arteriovenous crossings.[4,24,25] This has been hypothesized to occur due to thickening of the overlying artery, which causes narrowing of the vein, with subsequent vascular turbulence and endothelial damage contributing to venous thrombosis. The supertemporal quadrant is most commonly involved (58.1 percent of eyes), followed by the inferotemporal quadrant (29 percent) and outside of the temporal quadrants (12.9 percent).[3,25]

Eyes with more nonperfusion carry a greater risk of ocular neovascularization and a guarded visual prognosis.[26] CRVO generally causes greater degrees of vision loss and carries a more guarded prognosis. Abnormal new blood vessel growth can invade the iris, angle, optic nerve and retina. If the angle is involved, neovascular glaucoma can result. IOP elevation can occur within one month of onset or later, leading to the term "90-day glaucoma."[27]

With time, collaterization (retina-retina and retina-choroid anastomoses) can bypass the obstruction and improve clinical signs, and the hemorrhages, cotton wool spots and optic nerve edema can improve.

Imaging

While RVO is a clinical diagnosis, supplemental imaging can help confirm the diagnosis, monitor response to treatment and reveal complications such as macular edema and neovascularization.

Fluorescein angiography can illustrate the characteristic finding of delayed filling of the occluded retinal vein. In chronic cases, FA may only reveal microvascular changes, including microaneurysms and telangiectatic collateral vessels, after retinal hemorrhages have resolved. FA also permits visualization of peripheral capillary nonperfusion and

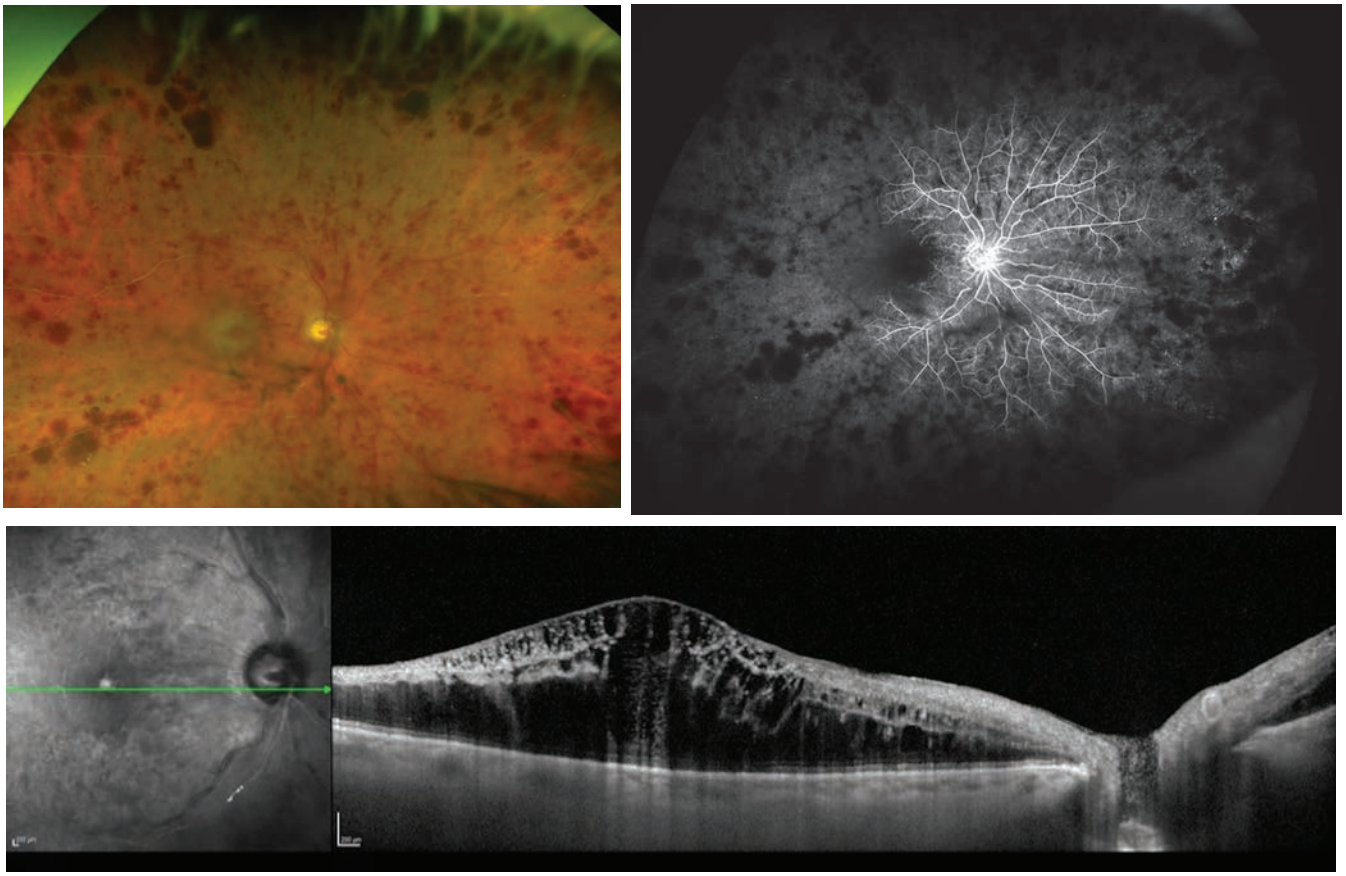

Figure 3. The patient from Figure 1, three months later. An ischemic CRVO has developed, as seen on the fundus photograph and fluorescein angiogram (top), with edema visible on OCT (bottom).

macular ischemia, and detection of subtle neovascularization that may not be clinically apparent. Historically, FA was also used to classify RVO into groups of perfused, nonperfused or indeterminate by evaluating for five or more disc areas of capillary nonperfusion in the Branch Vein Occlusion Study (BVOS), and ten or more disc areas in the Central Vein Occlusion Studies (CVOS).[26,28] According to the CVOS, CRVO were classified as ischemic if FA revealed more than 10 disc diameters of retinal capillary nonperfusion; they're considered perfused if fewer than 10 disc diameters of ischemia are present, or as indeterminate if accurate determination of the degree of nonperfusion can't be estimated due to significant retinal hemorrhage.[29] While this framework was useful for study purposes, it's been largely outdated with ultra-widefield imaging and its ability to help us easily detect nonperfusion and neovascularization.

Optical coherence tomography is critical in confirming the presence of macular edema, including cystoid changes and subretinal fluid, and monitoring response to treatment. Chronic cases can show ellipsoid zone loss from longstanding edema or ischemia. Images obtained with OCT can also provide additional information such as vitreoretinal interface abnormalities, neurosensory detachments and/or loss of outer retina integrity that may further limit vision or guide therapy. OCT angiography can also be helpful in diagnosing occult cases. OCTA allows imaging of the perfused retinal vasculature by acquiring high speed, sequential OCT A-scans at the same retinal locus and then processing complex digital subtraction algorithms to analyze differences created by the moving columns of blood. This technology can show a reduction of blood vessel density, mainly of the deep retinal plexus, in RVO.

Treatment

Unfortunately, no treatment can reverse RVO, though attempts have been made to create anastomoses through surgery and laser, to relieve the obstruction through thrombolytic administration and bypass the congestion via optic nerve sheathotomy.[30-33] As a result, the goal is to manage complications of macular edema and neovascularization.

Here, we'll discuss several landmark trials that help provide guidance in improving visual outcomes for both BRVO and CRVO. We'll also discuss the evolution of our treatment strategies, working our way from initial therapies that were used to our most current approaches.

• ***Laser for macular edema.*** The most common visually threatening

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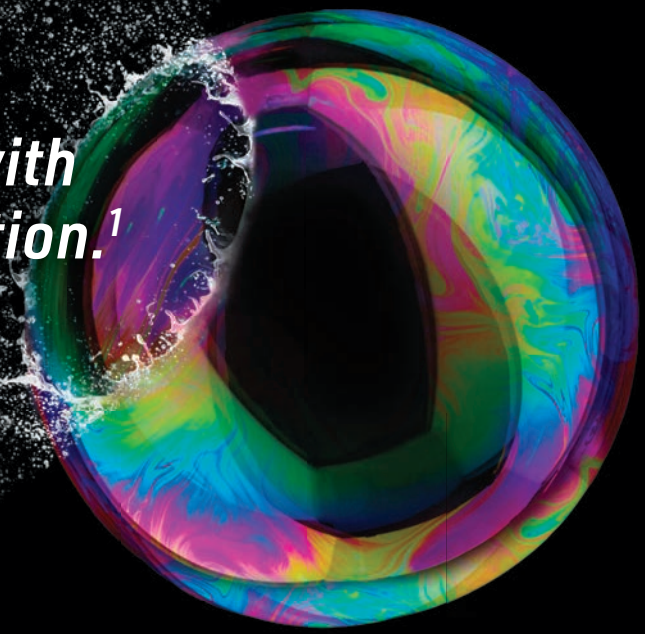

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Adverse Reactions

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

References: 1. Craig JP, Nelson JD, Azar DT, et al. *Ocul Surf.* 2017;15(4):802-812. **2.** Tyrvaya. Prescribing Information. Oyster Point Pharma; 2021.

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ADVERSE REACTIONS

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

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

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

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

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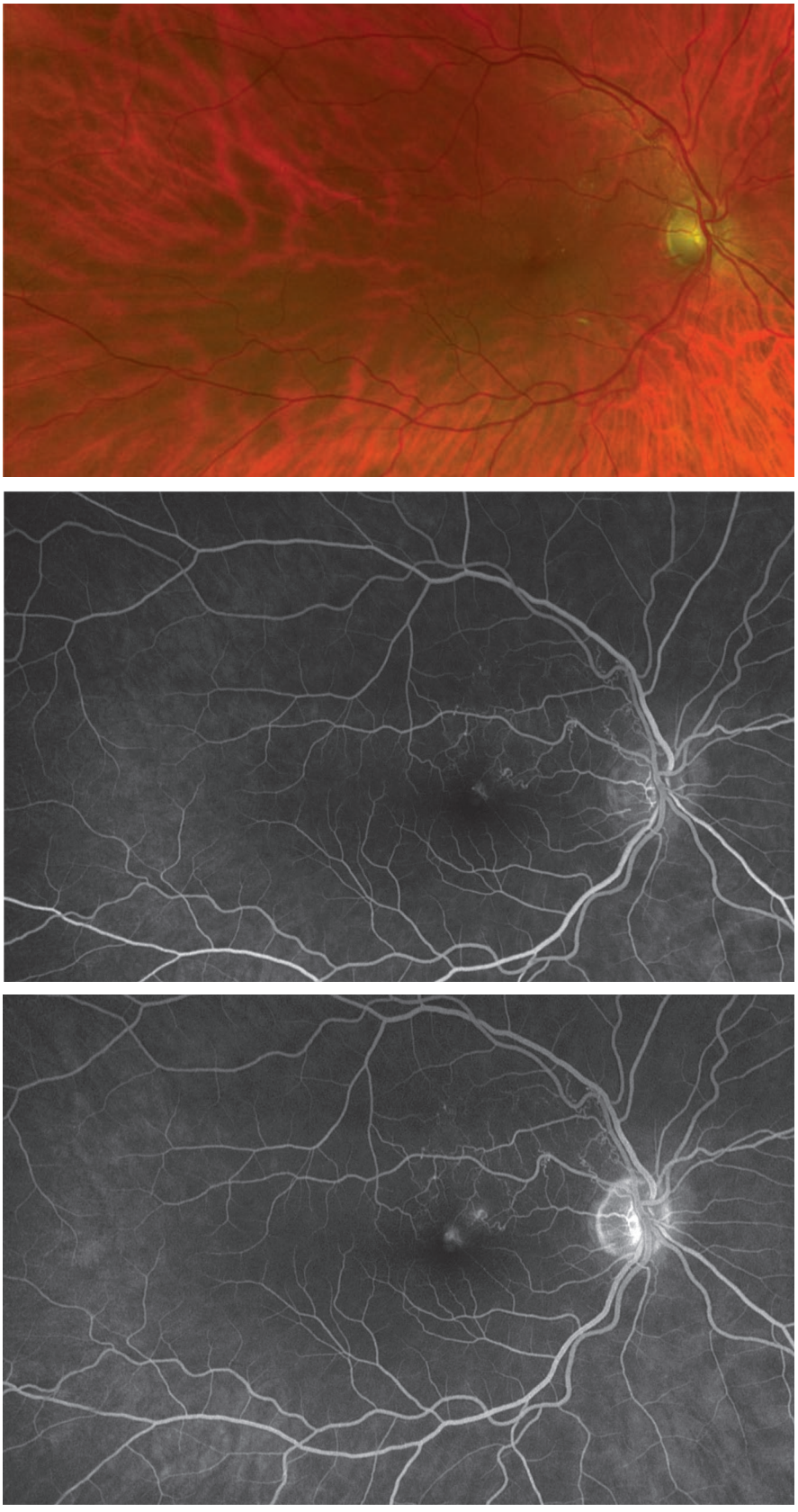

Figure 4. Fundus photograph and early (middle) and late (bottom) fluorescein angiograms showing twig branch retina vein occlusion.

complication of RVO is macular edema. In 1986, the National Eye Institute led the BVOS to examine laser treatment for ME from BRVO. In the study, researchers randomized patients with perfused BRVO and visual acuity of 20/40 or worse with ME to grid laser or observation. More patients gained two lines or more of visual acuity from baseline with laser than those without treatment (65 percent vs. 37 percent). Additionally, patients with laser were almost twice as likely to have a final visual acuity greater than 20/40. Given these findings, macular grid laser became the standard of care for ME associated with BRVO.[28] Interestingly, the CVOS demonstrated a lack of benefit with respect to the use of macular grid laser for ME in CRVO. While grid laser photocoagulation was historically the gold-standard treatment for BRVO, intravitreal pharmacotherapy has largely replaced laser as the intervention of choice for both BRVO and CRVO.

More recently, researchers have explored the use of peripheral "targeted" laser photocoagulation on angiographically nonperfused retina to decrease the burden of treatment associated with intravitreal anti-vascular endothelial growth factor injections. However, no study has demonstrated a benefit.[34-36]

• ***Intravitreal steroids for macular edema.*** Intravitreal corticosteroids are an effective treatment for ME secondary to RVO.[37-41] Use of intravitreal triamcinolone injection in the 2009 SCORE study resulted in superior visual outcomes in patients with CRVO compared to observation, but not compared to grid photocoagulation.[37,38]

The dexamethasone intravitreal implant 0.7 mg (Ozurdex; Allergan), in the GENEVA trial and in a head-to-head comparison versus ranibizumab in the COMRADE B and C trials, led to rapid visual acuity gain for two months (comparable to ranibizumab). However, visual acuity gain wasn't sustained after month

three in any of the trials, resulting in inferior overall performance compared to ranibizumab from month three to six.[39-41] These outcomes may be related to undertreatment in the dexamethasone arm compared to anti-VEGF therapy, however.[39-41] Also, it's well-known that intravitreal corticosteroids can be associated with ocular hypertension and cataract progression. Even so, some studies have shown that intravitreal steroids may be useful for the treatment of ME unresponsive to anti-VEGF therapy.[42,43]

• ***Intravitreal anti-VEGF therapy.*** Intravitreal injection of anti-VEGF agents has become first-line therapy for ME secondary to RVO since numerous prospective studies have revealed its remarkable therapeutic effects.[1,35,44–54] More than half of patients with nonischemic RVO will achieve rapid improvement in visual acuity and reduction in retinal thickness shortly after initiation of anti-VEGF therapy, and these improvements are largely maintained with adequate retreatment.[1,6-19,35,44-54] Early initiation (less than three months from onset) of anti-VEGF therapy appears to lead to the greatest improvement in visual acuity.[1,35,44-54]

There don't seem to be definitive differences in efficacy and safety among the different anti-VEGF agents.[1,55] Different injection frequency practices have been evaluated, however. The SHORE study demonstrated that an as-needed regimen with monthly follow-up, after seven monthly injections, was as effective as a monthly treatment approach.[49] Many of the pivotal trials have mandated a loading period, but other studies have shown that one or two injections may be enough before switching to PRN in cases where there has been complete ME resolution.[56] During initial therapy, follow-up intervals beyond two months aren't recommended. Visual acuity was maintained with bimonthly monitoring in the CRYSTAL study but not with quarterly monitoring in COPERNICUS.[50,54]

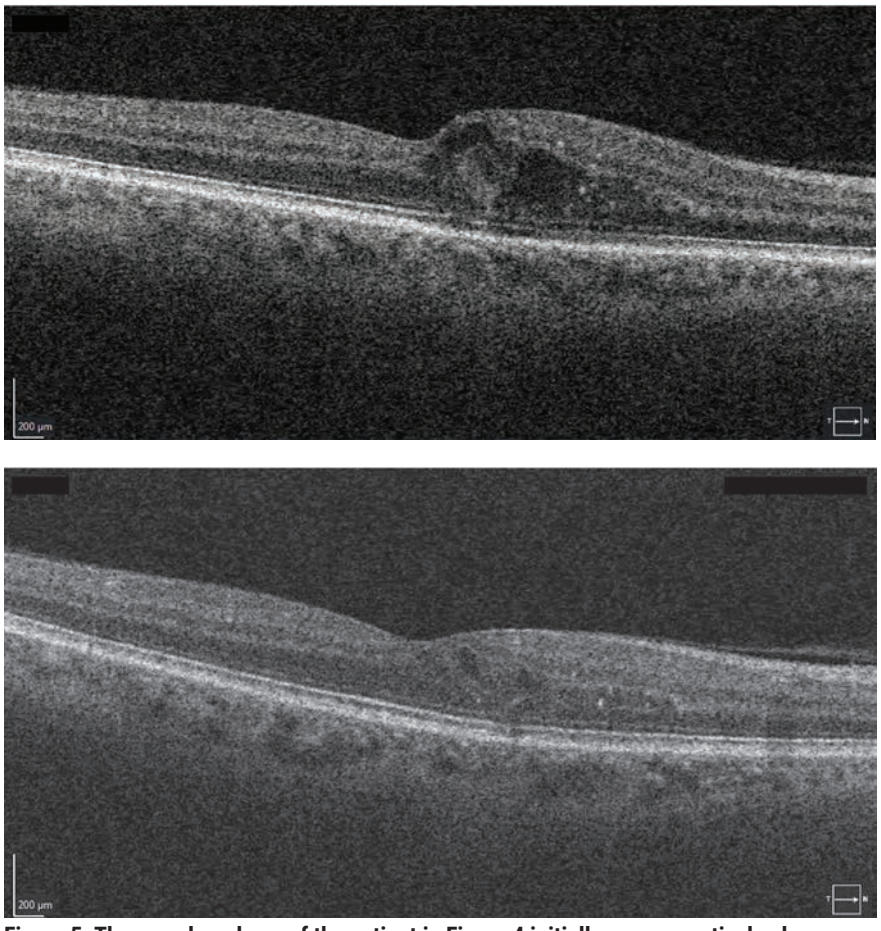

Figure 5. The macular edema of the patient in Figure 4 initially seen on optical coherence tomography (top) significantly improved on OCT one month after anti-VEGF treatment (bottom).

Other studies suggest that switching anti-VEGF agents, or switching to a steroid agent, should be considered in eyes that don't show a complete anatomic response.[57] Switching anti-VEGF agents, particularly to aflibercept (Eylea, Regeneron), may be beneficial for extending treatment intervals as well. In NEWTON and other studies, refractory ME unresponsive to ranibizumab (Lucentis, Genentech) or bevacizumab (Avastin, Genentech) was anatomically improved with aflibercept, and treatment intervals were able to be extended.[58-60]

Ongoing Studies

New therapeutics continue to be tested for macular edema. Two agents were recently tested in Phase III studies but, unfortunately, both studies were stopped.

Brolucizumab (Beovu, Novartis), an anti-VEGF injection approved for neovascular age-related macular degeneration, was being investigated in the Phase III RAPTOR and RAVEN studies for RVO; it included four-week dosing intervals. However, both studies were stopped, given safety concerns after higher rates of intraocular inflammation were seen in the brolucizumab group of another clinical trial with four-week dosing.[61] Additionally, the Phase III SAPPHIRE study examined suprachoroidal triamcinolone acetonide (Clearside) in conjunction with aflibercept for RVO but the combination didn't meet its primary endpoint compared to aflibercept alone so the study was stopped. Both of these agents showed prom-

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ise, given their new mechanisms of action and modes of delivery but, unfortunately, they weren't able to continue.[62]

Two agents are currently being investigated in Phase III studies for RVO. Faricimab (Genentech), a bispecific antibody targeting vascular endothelial growth factor-a and angiopoietin-2 is being investigated in the COMINO and BALATON RVO trials in comparison to aflibercept.[63] Additionally, KSI-301 (Kodiak Sciences), an anti-VEGF injection, is being compared to aflibercept in the Phase III BEACON study.[64]

Ocular Neovascularization

Besides macular edema, the other major visually threatening RVO complication is ocular neovascularization. Hypoxia and capillary nonperfusion can upregulate inflammatory cytokines, including VEGF, which promote increased vascular permeability and angiogenesis. The CVOS studied the risk of ocular neovascularization with and without pre-emptive panretinal photocoagulation, as determined by initial perfusion status. The study found that ocular neovascularization developed in 35 percent of ischemic or indeterminate eyes, compared with 10 percent of nonischemic eyes.[26] Preemptive PRP reduced the likelihood of ocular neovascularization, but prompt resolution of ocular neovascularization occurred more frequently when laser treatment was deferred.[26] Given these findings, the CVOS group recommended deferring PRP until ocular neovascularization develops.

Neovascular glaucoma has a guarded prognosis and treatment with PRP can be challenging if the patient is in pain, if there's significant corneal edema or if there's vitreous hemorrhage. Anti-VEGF medications can be used temporarily to treat neovascularization until PRP laser can be applied.

In conclusion, recognizing the clinical features of RVO and promptly treating the complications of macular edema and neovascularization is important to obtaining the best possible clinical outcomes. Unfortunately, there's no direct treatment for improving perfusion. Instead, our current treatment focuses on minimizing and managing the complications of macular edema and neovascularization. Good treatments exist, including anti-VEGF therapy, intravitreal corticosteroids and panretinal photocoagulation. Future directions for therapy include novel, longer-acting anti-VEGF agents and new drug delivery systems. ◀

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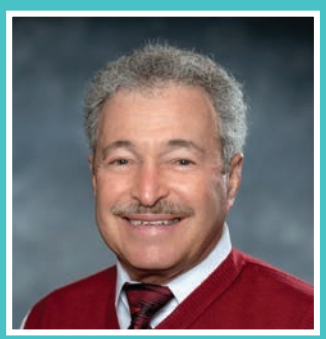

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PRESBYOPIA TREATMENT

First Presbyopia Drop Approved

Allergan/AbbVie announced FDA approval of Vuity (pilocarpine HCl ophthalmic solution) 1.25% for the treatment of presbyopia in adults, as the first FDA-approved drop to treat this condition. The company says that Vuity is a daily prescription drop that works as soon as 15 minutes after use and lasts up to six hours, as measured on day 30, "to improve near and intermediate vision without impacting distance vision." Vuity is a formulation of pilocarpine delivered with "pHast" technology, enabling the drop to rapidly adjust to the physiologic pH of the tear film, Allergan says.

The approval was based on data from two pivotal Phase III clinical studies, GEMINI 1 and GEMINI 2. In both studies, Allergan says, Vuity met the primary endpoint, reaching statistical significance in improvement in near vision in mesopic conditions without a loss of distance vision, versus the vehicle (placebo), on day 30 at hour three. Additionally, improvement was seen as early as 15 minutes and lasted through six hours. There were no serious adverse events observed in participants receiving Vuity in either the GEMINI 1 or GEMINI 2 study. The most common adverse events, occurring in less than 5 percent of patients, were headache and eye redness, the company says.

For more information, visit vuitypro.com.

OCULAR SURFACE

Dextenza Gets New Indication

Ocular Therapeutix announced that the FDA has approved its Supplemental New Drug Application to broaden the Dextenza label to add an additional indication for the treatment of ocular itching associated with allergic conjunctivitis. The intracanalicular insert lasts for up to 30 days, the company says. Dextenza is already approved to treat ocular pain and inflammation following ophthalmic surgery.

For information, visit bausch.com.

CONTACTS

Menicon Ienis

Menicon has released its first silicone hydrogel daily disposable contact lens. The company says the Miru 1day UpSide lens provides high oxygen availability and has an ultra-low modulus and a smooth, low-friction surface to promote eye health. The packaging ensures that the lens is always sitting convex-side up on a small bump to make handling the lens easier for patients, as well as minimizing risk of inner-lens contamination.

For information, visit meniconamerica.com.

TESTING AND PLANNING

Help for Detecting Oculomotor Dysfunction

If you want to improve the accuracy of your EOM exams—and reduce the time it takes to perform them—a new product from RightEye aims to help, the company says. Called RightEye Sensorimotor, the device is a tablet with an eye tracker and custom software that administers oculomotor tests and then produces documentation of the results.

Because the test can be run with minimal input from an operator, doctors are able to remove this element from their exams and delegate it to a technician in the pretest area, the company suggests.

The data generated can give clinicians better documentation of a patient's status upon identification of a problem, which can then be used as a baseline for comparison in follow-up visits, RightEye says.

For more information, visit RightEye.com.

Alcon Introduces Smart Cataract Software

Alcon recently released its Smart Solutions platform, starting with its Smart Cataract System. Using this software, surgeons and their staff can enter data once and have it carried forward throughout the office, from EHR systems to diagnostic equipment and surgical devices. The application connects data systems and most diagnostic devices—including the Argos Biometer with Image Guidance—with Alcon's cataract surgical equipment, including the LenSx Femtosecond Laser and LuxOR Revalia Ophthalmic Microscope, as well as commonly used microscopes and devices from other ophthalmic manufacturers. The company says that connecting biometry instruments with other medical records expedites surgical planning. Alcon says entering the data only once will also help eliminate transcription errors.

SMART Solutions makes use of the open, cloud-based infrastructure and services of Philips HealthSuite, built on Amazon Web Services, to enable surgeons to aggregate, organize and analyze all relevant data within a single, integrated application "designed for security and remote planning." Alcon is installing the system in several additional practices in the United States through the end of the year, and plans a broader rollout of Smart Cataract in 2022.

To learn more, visit AlconSMARTSolutions.com. ◀

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Phaco Technique and Endothelial Cell Loss

A randomized, single-blind noninferiority clinical trial, PERCEPOLIS, aimed to determine whether subluxation supracapsular phacoemulsification techniques were inferior to a reference endocapsular (divide-and-conquer) technique regarding postoperative corneal endothelial cell loss.

Patients (ages 18 years or older) with greater than +0.2 logMAR best spectacle-corrected visual acuity, and normal-to-severe density cataract were randomized to subluxation or divide-and-conquer phacoemulsification in 2015 and 2016. Follow-up with ophthalmic tests was conducted on day four; and months one, three and 12. The primary study outcome was ECL at all time points. Secondary study endpoints were operative variables, including effective phaco time and procedure duration. A clinically relevant noninferiority ECL limit was established based on the literature.

Here are some of the findings:

- In total, 292 patients (mean age, 73 years; 59 percent female) were randomized and underwent subluxation (n=148) or divide-and-conquer (n=144).
- Day four, and months one, three and 12 data were available for 243, 270, 275 and 198 patients, respectively.
- The unexpectedly high dropout at 12 months meant that the 12-month ECL data could only be assessed qualitatively.
- Surgery was successful in all patients.
- Subluxation was noninferior to divide-and-conquer in ECL.
- Effective phaco times were similar, but subluxation was associated with shorter procedure duration.

Scientists found the subluxation technique was noninferior to divide-and-conquer regarding postoperative ECL, at least in the first three months, and was associated with reduced intervention time. They added that subluxation techniques may be suitable alternatives to endocapsular techniques.

Cornea 2021; Nov 3.
[Epub ahead of print]
Perone JM, Ghetemme C, Zevering Y, et al.

Symptoms Associated with VF Damage in Glaucoma

Researchers studied which patient-reported symptoms best distinguished patients with and without glaucoma, and which explained the most variance in visual field damage. They also compared the amount of variance that can be explained by symptoms vs. retinal nerve fiber layer thickness, as part of a cross-sectional study. Participants included adults diagnosed with glaucoma or suspicion of glaucoma (controls).

Worse-eye VF damage was defined by perimetric testing; RNFL thickness was defined by OCT imaging. Patients rated their visual symptoms on questions collated from several published questionnaires, rating the frequency and severity of 28 symptoms on a scale of one (never/not at all) to four (very often/severe). Multivariable regression models identified patient-reported symptoms that were associated with the highest variance in VF damage.

Main outcome measures included patient-reported symptoms that explained the most variance in VF damage and RNFL thickness.

A total of 170 patients (mean age=64; 58 percent female; 47 percent employed) completed testing, including 95 glaucoma suspects and 75 glaucoma patients.

Here are some of the findings:

- In glaucoma patients, median mean deviation of VF damage in the worse eye was -19.3, and ranged from -5.3 to -34.7 dB.
- Symptoms more common among glaucoma patients compared to glaucoma suspects included:
  — better vision in one eye;
  — blurry vision, glare;
  — sensitivity to light;
  — cloudy vision; and
  — little peripheral vision.
- Worse severity ratings for the symptom "little peripheral vision" explained the most variance in VF damage (43 percent).
- A multivariable model including the frequency of cloudy vision, severity of having little peripheral vision, missing patches of vision, one eye having better vision and vision worsening, plus sociodemographic features, explained 62 percent of the variance in VF damage.
- Comparatively, a multivariable model of worse-eye RNFL thickness and sociodemographic features explained 42 percent of the variance in VF damage, while a model including only sociodemographic features explained 8 percent of the variance in VF damage.

Researchers found that five patient-reported symptoms explained a significant amount of the variance in VF damage. They suggested that asking patients about their symptoms may optimize patient-physician communication and be a useful adjunct

to clinical testing in some patients to estimate disease severity.

Ophthalmology 2021; Oct 27. [Epub ahead of print]
Shah YS, Cheng M, Mihailovic A, MS, et al.

Trapezoid vs. Conventional 2.2-mm Clear Corneal Incisions

Scientists compared the incidence of incision-related Descemet's membrane detachment among eyes undergoing modified vs. conventional 2.2-mm incision phacoemulsification for hard nuclear age-related cataract.

The double-masked, parallel randomized clinical trial was conducted from July 22, 2019, to January 22, 2020, at Zhongshan Ophthalmic Center, Sun Yat-sen University in Guangzhou, China. The study included patients with age-related cataract and nuclear opalescence grade of 4.0 or greater based on the Lens Opacities Classification System III. Patients were enrolled in this study according to the following inclusion criteria: age between 65 to 90 years; pupil size of 6 mm or greater after dilation; Lens Opacities Classification System III nuclear opalescence grade of 4.0 or more; and corneal endothelial cell density greater than 1,500 cells/mm^2.

Main outcomes and measures included incidence of incision-related DMD at postoperative day 1.

A total of 130 eyes of 130 patients were randomized into the conventional group (n=65) or the modified group (n=65). The mean age of participants was 74.5 ±5.9 years and 74.3 ±6 years in the conventional and modified groups, respectively. A total of 26 participants in the conventional group (40 percent) and 27 in the modified group (42 percent) were men. Here are some of the findings:

- Compared with eyes in the conventional group, the incidence of DMD in eyes in the modified group was significantly lower at postoperative day one (difference, 26.15; CI, 9.60 to 42.71; p=0.003).
- The difference at postoperative day seven was 16.92 (CI, 2.91 to 30.94; p=0.02).
- The length of DMD (postoperative day one: difference, 0.188; CI, 0.075 to 0.301; p=0.002) and maximal corneal thickness at incision site (postoperative day 1: difference, 0.032; CI, 0.006-0.057; p=0.02; postoperative day 7: difference, 0.019; CI, 0.003 to 0.035; p=0.02) were lower in the modified group, while visual quality parameter modulation transfer function (postoperative day one: difference, -0.033; CI, -0.064 to -0.001; p=0.04) was higher.

> **Findings suggest that phaco with a modified 2.2-mm trapezoid incision may reduce the incidence of DMD in hard nuclear age-related cataract on postop day one.**

- No difference was observed between the two groups in best-corrected visual acuity, central corneal endothelium loss or surgically induced astigmatism at any follow-up time.
- No intraoperative complications were reported in either group.

Scientists wrote that the findings suggested that modified 2.2-mm trapezoid incision phacoemulsification reduced the incidence of DMD for hard nuclear age-related cataract at postoperative day one and might be considered in patients at high risk of incision-related DMD, although they added that the clinical relevance couldn't be determined with certainty from this trial.

JAMA Ophthalmol 2021; Oct 14. [Epub ahead of print]
Dai Y, Liu Z, Wang W, et al.

Vascular Issues and Low-tension Glaucoma

Researchers from the Mayo Clinic Department of Ophthalmology undertook a retrospective, case-control study designed to identify patients seen at the clinic between 2005 and 2015 with low-tension glaucoma, and an age- and sex-matched control group, each containing 277 patients.

The low-tension glaucoma group had more myopic refractive errors in diopters (-1.6 vs. -1.0, p<0.001), lower intraocular pressure (14.2 vs. 15.2 mmHg, p<0.001), and a higher cup-to-disc ratio (0.7 vs. 0.3, p<0.001).

The low-tension glaucoma group was significantly less likely to be obese (BMI >30, p=0.03). They had a significantly higher prevalence of systemic hypertension (OR: 1.64, p=0.004), diabetes mellitus (OR 3.01, p≤0.001), peripheral vascular disease (OR 2.61, p=0.009), migraine headache (OR 2.12, p=0.02), anemia (OR 2.18, p=0.003), systemic hypotension (OR 4.43, p≤0.001), Raynaud's Syndrome (OR 3.09, p=0.05), angiotensin converting enzyme inhibitor (OR 1.64, p=0.01), and calcium channel blocker use (OR 1.98, p=0.004).

After adjusting for systemic hypertension, calcium channel blocker use remained significant (OR 1.70, p=0.03). No significant difference was found with respect to hyperlipidemia, obstructive sleep apnea, coronary artery disease, carotid stenosis, stroke, or use of statins, ACE inhibitors, angiotensin receptor blockers, beta blockers or metformin.

Multiple vascular-associated conditions were associated with low-tension glaucoma, including systemic hypertension, diabetes mellitus, peripheral vascular disease, migraine headaches, Raynaud's Syndrome, anemia, systemic hypotension, and calcium channel blocker use. The researchers say that this study strengthens evidence for the vascular hypothesis of low-tension glaucoma. ◀

Journal of Glaucoma; Nov. 03. [Epub ahead of print]
Funk RO, Hodge DO, Kohli D, et al.

Years after LASIK, a 36-year-old patient presents with an injury to his right eye.

KAYLENE CARTER, MD, AND CHRISTOPHER J. RAPUANO, MD
PHILADELPHIA

Presentation and Initial Work-up

A 36-year-old male was referred to Wills Eye Hospital for evaluation of poor vision after an injury to his right eye. He had undergone LASIK in India in both eyes 10 years prior, with subsequent trauma to the right eye from a 3x5 index card one year afterwards. He was seen and evaluated by multiple ophthalmologists, initially undergoing a trial of rigid gas permeable lenses which were stopped due to discomfort. He reported that vision in the right eye had been poor since the injury; vision in the left eye had been stable. At the time of evaluation, he denied pain, redness or discharge.

Medical History

Past medical history was noncontributory and he had no other surgical history. Family history was negative for chronic conditions. He denied alcohol, tobacco and illicit drug use.

Exam

Uncorrected visual acuity was 20/400 in the right eye, without improvement with refraction but with pinhole improved to 20/150, and 20/20 in the left eye. Pupillary examination was normal and confrontational visual fields and extraocular movements were full bilaterally. Intraocular pressure was within normal limits bilaterally.

Anterior slit lamp examination of the right eye showed a LASIK flap with significant gray-white opacities in the flap interface measuring 5.7 x 2.3 mm, an iron line, an irregular corneal surface and a missing flap inferiorly *(Figure 1)*. Anterior slit lamp examination of the left eye was unremarkable, and showed a LASIK flap without abnormalities.

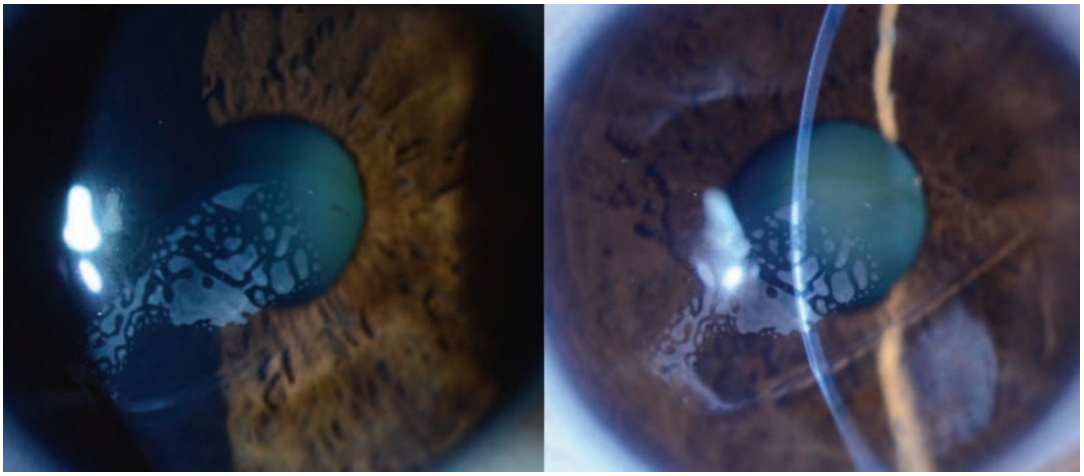

Figure 1. Slit lamp examination showing a large area of gray-white opacities in the LASIK flap interface, an iron line, missing flap inferiorly and irregular corneal curvature.

What is your diagnosis? What further work-up would you pursue? The diagnosis appears on p.72.

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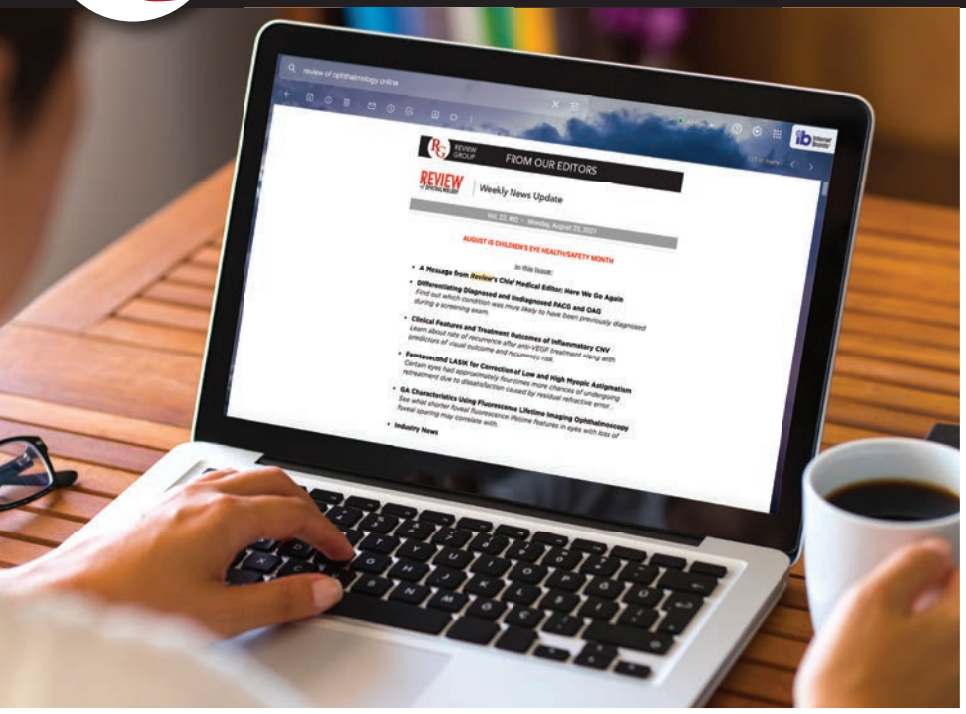

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REVIEW GROUP — FROM OUR EDITORS

REVIEW of OPHTHALMOLOGY — Weekly News Update

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

AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

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

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

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

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Work-up, Diagnosis and Treatment

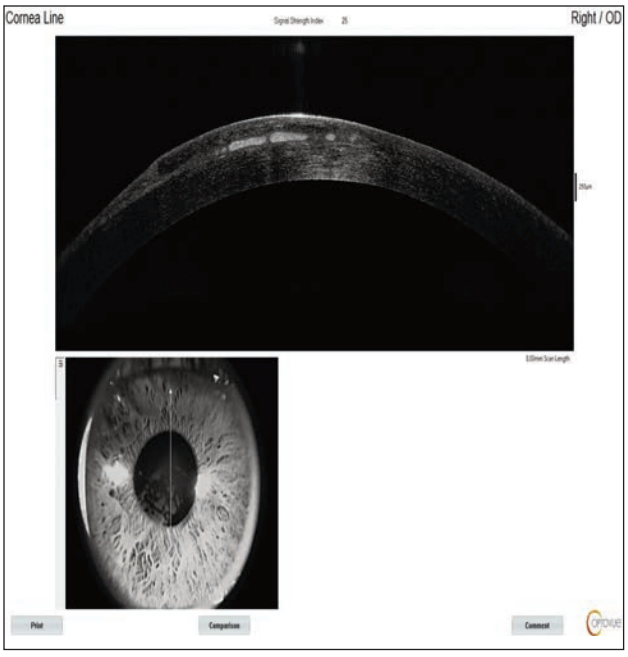

Figure 2. AS-OCT demonstrating an irregular LASIK flap and anomalous tissue within the flap interface.

Anterior segment optical coherence tomography revealed an irregular corneal flap and anomalous tissue within the flap interface *(Figure 2)*. Corneal topography and tomography maps showed significant irregular astigmatism and an area of inferior steepening at the inferior paracentral zone, with inferotemporal thinning *(Figure 3)*.

Based on clinical and multimodal imaging features, the patient was found to have significant epithelial ingrowth with a partially missing LASIK flap in the right eye. He was presented with options to manage clinically significant epithelial ingrowth, including observation, rigid gas permeable contact lens, scleral lens, laser treatment, attempting to lift the flap and scrape the epithelial ingrowth, amputate the flap and treat with mitomycin C, and partial- or full-thickness corneal transplant. He elected to avoid surgery and observe for now, with frequent evaluation for progression, approximately every six months.

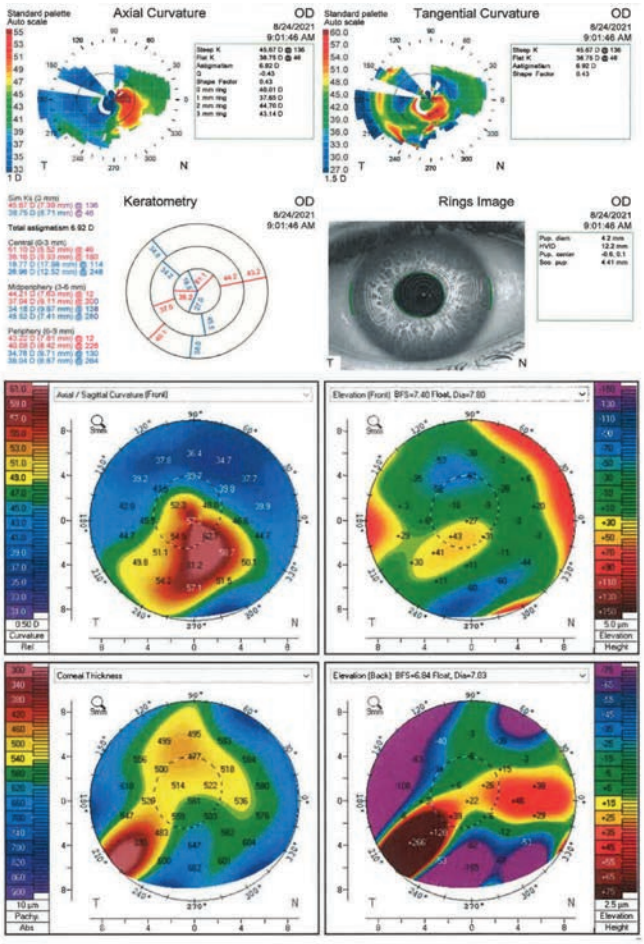

Figure 3. Topography and tomography maps demonstrating significant irregular astigmatism.

Discussion

Post-LASIK epithelial ingrowth is due to the growth of surface epithelial cells under the LASIK flap, resulting from poor flap adhesion and subsequent invasion of the epithelial cells. When severe enough, patients commonly experience blurred vision, glare or halos, visual distortion, pain and/or foreign body sensation. Diminished visual acuity results from these cells causing irregular astigmatism, frank opacity in the visual axis, and/or decreased nutrition delivery to healthy keratocytes, resulting in stromal melt.

Clinically significant epithelial ingrowth is a relatively uncommon complication after primary LASIK; one study found an incidence of 0 percent in 3,866 cases.[1] The most common etiologic factor is LASIK retreatment, with an incidence ranging from 2 percent to 20 percent.[1–3] In particular, clinically significant ingrowth seems to occur more frequently when LASIK retreatment is performed three or more years after primary LASIK.[1] In the post-LASIK setting, decreased visual acuity may also be secondary to other interface complications such as infectious keratitis and diffuse lamellar keratitis; thus, epithelial ingrowth must be distinguished from these conditions. Epithelial ingrowth is

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generally easily distinguishable on slit lamp examination due to the appearance of nests of cells at the flap interface.

Potential risk factors for epithelial ingrowth include: the method of flap creation; flap thickness; a postoperative epithelial defect; diffuse lamellar keratitis; epithelial basement membrane dystrophy; a history of recurrent erosions; chronic eye rubbing; Meibomian gland disease; and especially flap trauma.[4,5,6,7] Femtosecond-laser-assisted flaps have been shown to result in less epithelial ingrowth than mechanical microkeratome flaps, which may be related to the anatomy of the flap edge.[4,8]

> **Severity of epithelial ingrowth is highly variable; it can be asymptomatic, self-limited or clinically significant and in need of treatment for irregular astigmatism and prevention of flap melt.**

Severity of epithelial ingrowth is highly variable; it can be asymptomatic, self-limited or clinically significant and in need of treatment for irregular astigmatism and prevention of flap melt.[9] One review of 55 eyes with post-LASIK epithelial ingrowth showed that mild epithelial ingrowth may be safely observed, while significant epithelial ingrowth that reaches several millimeters towards the pupillary margin can respond well to removal.[10] Treatment may be categorized as non-surgical, laser or surgical. Laser treatment includes yttrium-aluminum-garnet (YAG) laser, which, when applied to the region of ingrowth, creates gas bubbles that destroy the epithelial ingrowth cells.[7]

Surgical options include flap lift and mechanical scraping, flap removal and even partial- or full-thickness corneal transplantation.[11] Flap lift and scraping is commonly used, and involves mechanical debridement of the posterior flap and stromal bed. However, recurrence after flap lift and scraping is relatively high, at 23 to 36 percent.[2,5] Application of alcohol after flap lift and scraping has been employed to destroy residual epithelial cells, but this can also be damaging to the cornea. Excimer laser phototherapeutic keratectomy of the interface has also been used in an attempt to eliminate residual epithelial cells, but it can result in irregular astigmatism. Mitomycin C may also be used to reduce corneal haze. Suturing the flap edge after mechanical scraping of the interface is often successful in treating epithelial ingrowth.[10] Additional use of hydrogel sealant or fibrin glue as an adjunct after thorough debridement may also be helpful in preventing recurrence.[12–16]

A complication to be aware of with epithelial ingrowth is the possibility of corneal flap melt, which can occur in as little as two weeks' time. It's thought to be secondary to lack of nutrients reaching the flap and/or collagenase that's released from hypoxic epithelial cells underneath the flap. In this patient, the missing portion of inferior flap may have been a result of flap melt from a prolonged period of epithelial ingrowth.

In summary, we describe a patient with clinical and imaging findings of severe epithelial ingrowth with a portion of missing LASIK flap years after eye trauma. We summarize the disease pathogenesis, risk factors and multitude of management options for this condition. While there is no one-size-fits-all treatment for this condition, depending on the severity and location of epithelial ingrowth, there are promising options for managing it. ◀

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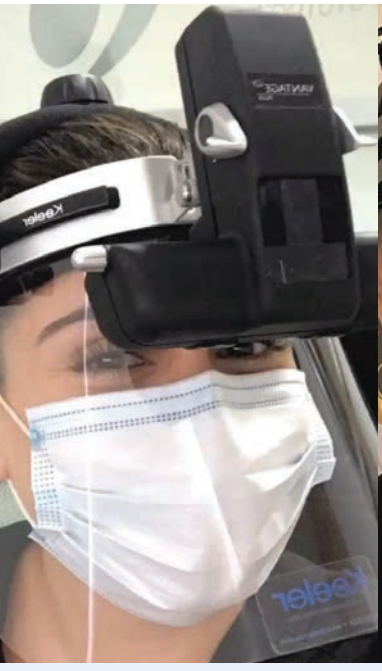

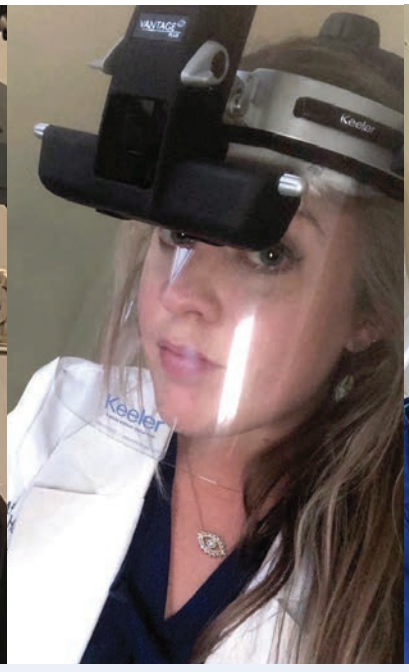

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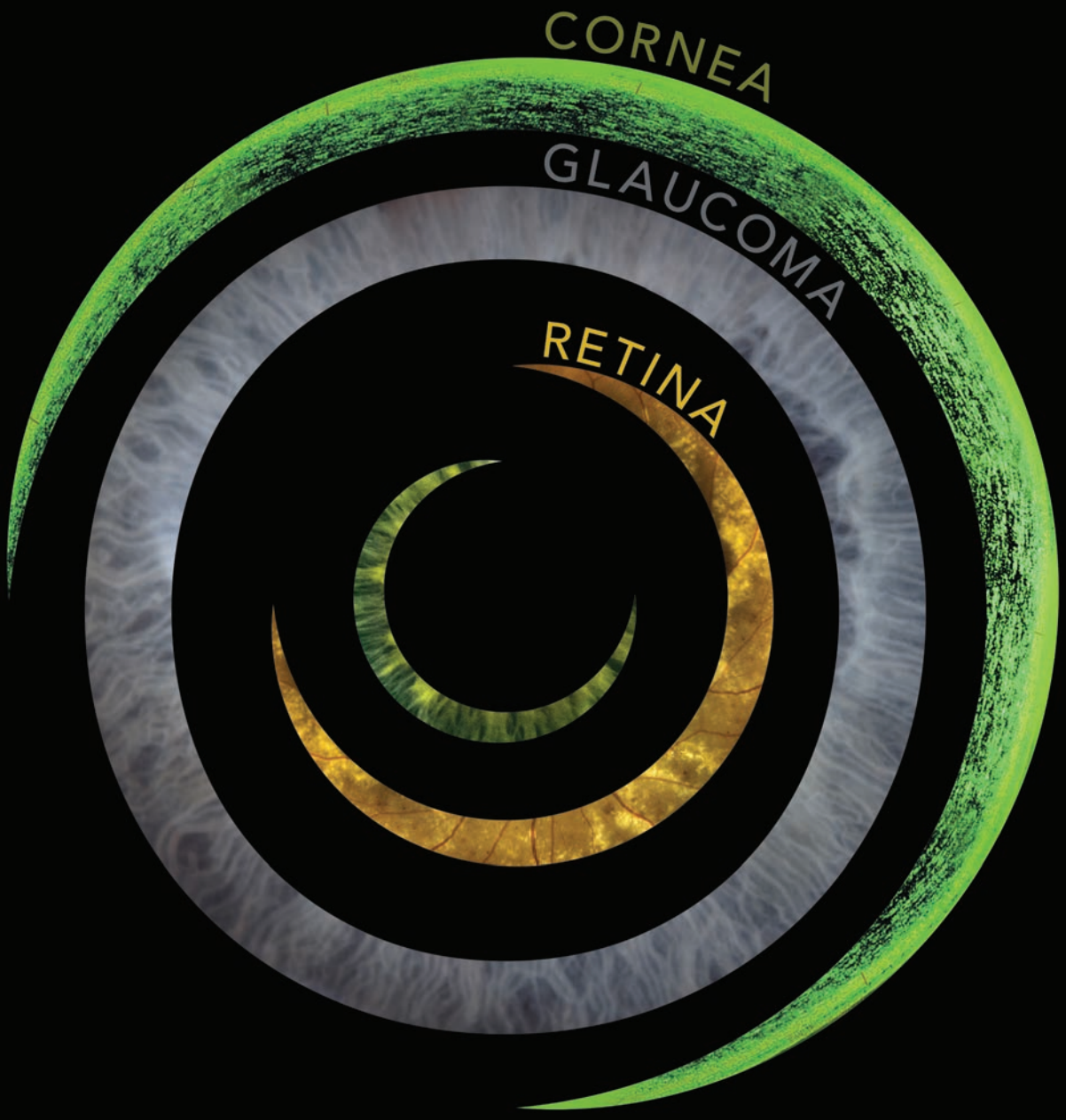

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