Wills Eye Resident Series: A woman presents with vascular sheathing and floaters, *p. 80*

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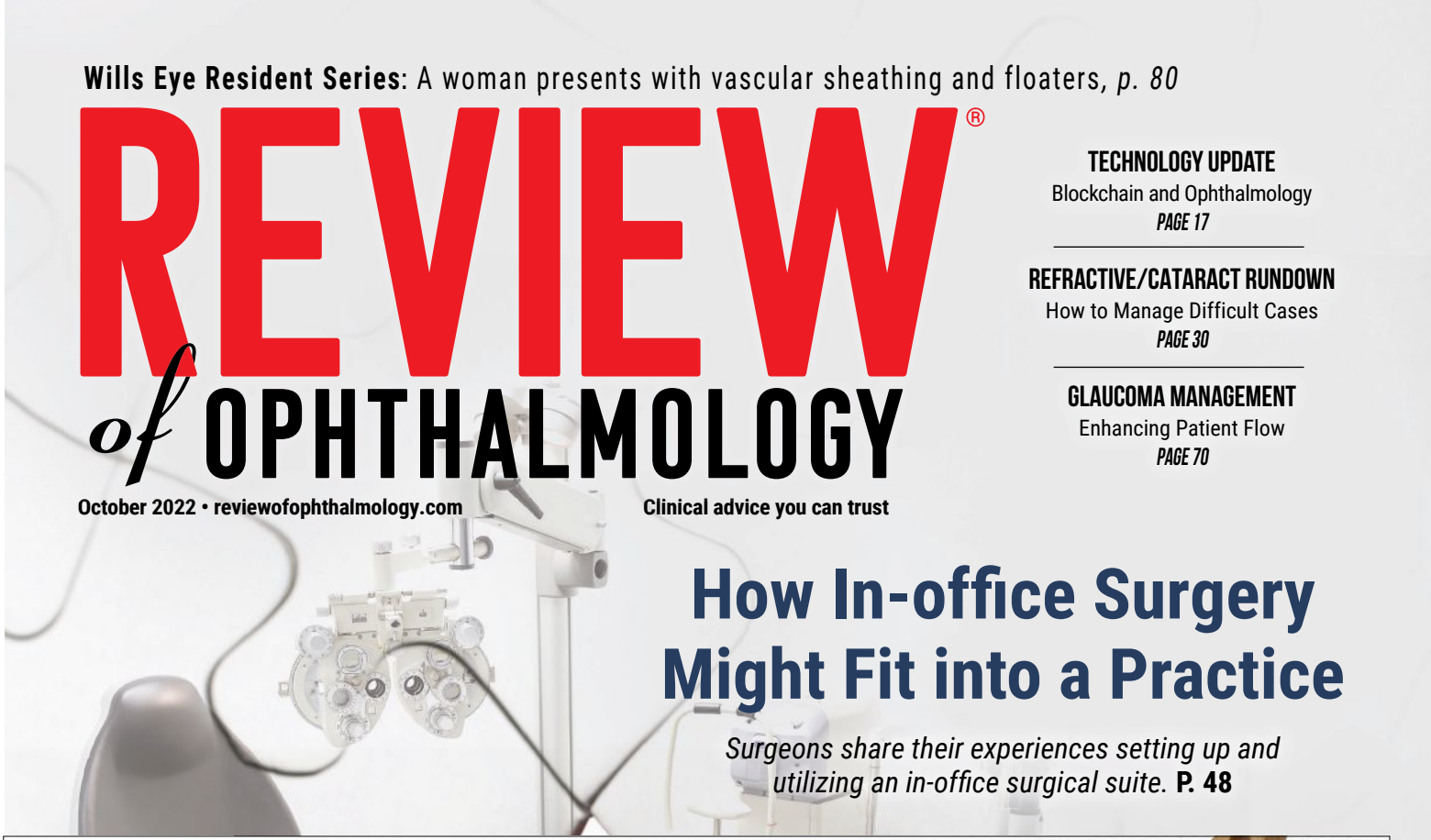

How In-office Surgery Might Fit into a Practice

Surgeons share their experiences setting up and utilizing an in-office surgical suite. **P. 48**

New from the makers of the #1-prescribed dry eye brand in Europe*

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- Suitable for all dry eye sufferers, including contact lens wearers†

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Request samples and learn more by scanning the QR code or visiting iVIZIA.com/ECP.

*Prescription market data, Sept. 2021 – S01K without cyclosporine.
†To limit blurriness when using contact lenses, remove contacts, apply drops, then insert contacts.

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References: 1. Chen W, Zhang X, Liu M, et al. Trehalose protects against ocular surface disorders in experimental murine dry eye through suppression of apoptosis. *Exp Eye Res*. 2009;89(3):311-318. **2.** Aragona P, Colosi P, Rania L, et al. Protective effects of trehalose on the corneal epithelial cells. *ScientificWorldJournal*. 2014;2014:717835. **3.** Chiambaretta F, Doan S, Labetoulle M, et al. A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome. *Eur J Ophthalmol*. 2017;27(1):1-9. **4.** Liu Z, Chen D, Chen X, et al. Trehalose induces autophagy against inflammation by activating TFEB signaling pathway in human corneal epithelial cells exposed to hyperosmotic stress. *Invest Ophthalmol Vis Sci*. 2020;61(10):26. **5.** US FDA Department of Health and Human Services. Ophthalmic drug products for over-the-counter human use. Updated October 21, 2021. Accessed January 19, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349. **6.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15(3):575-628. **7.** Schmidl D, Schmetterer L, Witkowska KJ, et al. Tear film thickness after treatment with artificial tears in patients with moderate dry eye disease. *Cornea*. 2015;34(4):421-426.

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ALSO INSIDE:

- The Latest Ways to Treat Dry Eye **P. 36**
- Pearls for Dry-Eye Diagnosis **P. 44**
- Tips for Interpreting OCT Images **P. 58**

REVIEW OF OPHTHALMOLOGY VOL. XXIX, NO. 10 • OCTOBER 2022 • IN-OFFICE SURGERY • DRY-EYE TREATMENT • DIAGNOSING DRY EYE • INTERPRETING OCT

xiidra® (lifitegrast ophthalmic solution) 5%

When Selecting an Rx Treatment for Dry Eye Disease

DON'T MAKE HER WAIT. CHOOSE XIIDRA.

Because lasting symptom relief can start as early as 2 weeks[1*†]

*Xiidra reduced symptoms of eye dryness at 2 weeks (based on Eye Dryness Score [EDS] compared to vehicle) in 2 out of 4 studies, with improvements observed at 6 and 12 weeks in all 4 studies.[1]

Access to Xiidra is better than ever.[2]
Scan to see coverage in your area.

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

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080


Not an actual patient.

Important Safety Information (cont)

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

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

†**Pivotal trial data**

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

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

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

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

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

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

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

6.2 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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VOLUME XXIX • NO. 10

OCTOBER 2022

AMA Joins Plaintiffs in Lawsuit Against Cigna

In September, the American Medical Association along with two other physician organizations joined a class-action lawsuit against health-care insurer Cigna. The lawsuit alleges that Cigna underpaid health insurance claims filed by providers in the MultiPlan network.[1]

The suit was brought against Cigna in June by three plaintiffs who had become exposed to balance billing as a result of Cigna's misconduct. Each of the plaintiffs in *Stewart et al. v. Cigna Corporation et al.* had internal appeals filed on their behalf, and all were denied.

MultiPlan is the nation's largest third-party network company, and it contracts with more than 1.2 million providers in the United States. When providers enter into contracts with MultiPlan, they agree to accept a set percentage of the total billed charges as payment in full and also agree not to hold patients liable for the balance. These participating providers also indirectly contract with Cigna since Cigna contracts with MultiPlan to gain access to their provider network.

The suit alleges that Cigna breached its fiduciary duties, including its duty to honor the written plan's terms and its duty of loyalty, as the company seems to have put its own economic interests before that of plan member patients. According to the case, Cigna is required to reimburse MultiPlan's participating providers at the in-network amount, but the insurance company instead applied "lower reimbursement methodology" to pay those providers less, as if they were out-of-network. This left patients "exposed to the threat of balance billing," says the suit.

For fully insured plans, Cigna keeps more money by paying less in benefits. For self-funded plans such as those of the class representatives, Cigna's misconduct enabled it to receive higher administrative fees. "Cigna receives a 'savings' fee, payable by its self-funded customers, that is larger when Cigna causes the Plan to pay less for a given claim," the lawsuit explains. "By paying less than the amount required by the MultiPlan Contract, Cigna increases the amount of 'savings' it claims and the resulting fees it receives."

The lawsuit seeks to represent all who are insured under a Cigna plan governed by the Employee Retirement Income Security Act (ERISA) and who see MultiPlan providers who are indirectly contracted with Cigna.

American Medical Association President Jack Resneck Jr., MD, said in a statement that "Cigna's misconduct is riddled with conflicts of interest and manipulations that routinely shortchanged payments to MultiPlan Network physicians and interfered with the patient-physician relationship by ignoring the MultiPlan contracts and making incorrect statements to patients about their liability for the unpaid portion of the billed charges.

"Patients and physicians have a right to expect health insurers to uphold their promise to provide fair and accurate payment for medical services," he continued. He says that by joining the lawsuit as a plaintiff, the American Medical Association hopes to "shed light on Cigna's misconduct and create remedies so that patients and physicians can look forward to getting what they are promised."

Cigna could not be reached for comment.

1. Stewart v. Cigna. U.S. District Court for the District of Connecticut. Case 3:22-CV-00769. Filed June 10, 2022. https://www.classaction.org/media/stewart-et-al-v-cigna-corporation-et-al.pdf. Accessed September 20, 2022.

THE CIGNA LAWSUIT: WHO'S INVOLVED?

The class-action lawsuit *Stewart v. Cigna* was filed on June 10, 2022, and is pending in the Connecticut District Court. It involves the following:

Plaintiffs
- Stewart, Plumacher and Cardona as class representatives
- American Medical Association
- Washington State Medical Association
- Medical Society of New Jersey

Defendants
- Cigna Corporation
- Cigna Health and Life Insurance Company

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REFERENCE

1. Glaukos Data on File.

iStent infinite® IMPORTANT SAFETY INFORMATION

INDICATION FOR USE. The iStent infinite® Trabecular Micro-Bypass System Model iS3 is an implantable device intended to reduce the intraocular pressure (IOP) of the eye. It is indicated for use in adult patients with primary open-angle glaucoma in whom previous medical and surgical treatment has failed. **CONTRAINDICATIONS.** The iStent infinite is contraindicated in eyes with angle-closure glaucoma where the angle has not been surgically opened, acute traumatic, malignant, active uveitic, or active neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent infinite is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. Three out of 61 participants (4.9%) in the pivotal clinical trial were phakic. Therefore, there is insufficient evidence to determine whether the clinical performance of the device may be different in those who are phakic versus in those who are pseudophakic. **ADVERSE EVENTS.** The most common postoperative adverse events reported in the iStent infinite pivotal trial included IOP increase ≥ 10 mmHg vs. baseline IOP (8.2%), loss of BSCVA ≥ 2 lines (11.5%), ocular surface disease (11.5%), perioperative inflammation (6.6%) and visual field loss ≥ 2.5 dB (6.6%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

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PM-US-0909

GLAUKOS

(Continued from p. 5)

More Bad News for Smokers' Eye Health

There are few health and ocular conditions not impacted by frequently smoking tobacco. In glaucoma, smoking is known to be a risk factor; however, until now, research on the association between smoking and disease progression had been lacking. Findings of the new longitudinal study revealed that higher smoking intensity is associated with faster rates of retinal nerve fiber layer thinning.

The patients included in the investigation had primary open-angle glaucoma, at least three years of follow-up and five visits with OCT scans. There were 466 eyes of 314 patients in the analysis, all with follow-ups between 6.4 and 6.7 years. Smoking intensity was calculated as packs per year as reported at the baseline OCT visit.

The researchers noted that 39 percent of the patients reported a history of smoking and that the average smoking intensity was 16.5 packs per year. The data showed that greater smoking intensity was significantly associated with faster RNFL thinning (-0.06 µm/year per 10 packs/year increase) after adjusting for all other factors including alcohol consumption, BMI and race, none of which showed an association. They wrote in their paper, "Specifically, when smoking intensity is greater than eight packs per year, smoking intensity was associated with faster RNFL thinning in patients with glaucoma."

The patients who had a slower rate of RNFL thinning over the study period smoked a mean of 15.1 packs per year, while those with a moderate to fast rate of thinning had a mean smoking intensity of 24.3 packs per year. In patients who smoked previously, 20.7 percent were classified with at least a moderate rate of RNFL thinning. Considering this finding, the researchers suggest it would be helpful if future studies focused on whether smoking cessation can reduce glaucoma.

Because patients who smoke may be at higher risk of faster and irreversible progression potentially leading to vision loss, the researchers concluded, "As with other risk factors for glaucoma, the smoking status of a patient can help guide both the frequency of monitoring and the glaucoma therapy."

Nishida T, Mahmoudinezhad G, Weinreb RN, et al. Smoking and progressive retinal nerve fiber layer thinning in glaucoma. Br J Ophthalmol. September 13, 2022. [Epub ahead of print].

Strokes and the Prevalence of Ocular Disease

A cross-sectional study was recently conducted to better understand the relationship between stroke and ocular disease. Significant associations between visual impairment and major ocular disease with stroke were observed in this national study population. The study included 4,570 participants in the 2005-2008 National Health and Nutrition Examination Survey.

With an odds ratio of 5.54, ocular disease was associated with stroke, most notably in the form of cataract (30.8-percent prevalence among stroke patients vs. 13.4 percent without), AMD (19.6 vs 7.2 percent) and diabetic retinopathy (26.6 vs 11.6 percent). Following adjustments for age and gender, an odds ratio of 9.61 was observed among stroke patients with diabetic retinopathy. Additionally, the study authors reported odds ratios for mild to moderate and severe visual impairment of 6.79 and 9.46, respectively, after adjusting for age and gender.

The study authors noted that the associations were limited to mild visual impairment, mild-to-moderate and severe visual impairment and any ocular disease. The data also revealed significant associations between diabetic retinopathy and any ocular disease in diabetic participants. The researchers identified a close relationship between stroke and mild-to-moderate and severe visual impairment among individuals with hypertension.

"Despite impaired central vision, which is the most common visual impairment in stroke patients, eye movement disorders, visual field loss and visual perceptual disorders are also usually found among stroke patients, and most patients have a combination of several visual problems," the authors wrote in their paper to be published in the journal *Eye*.

"Our cross-sectional study shows stroke is associated with increased prevalence of ocular diseases," the study authors noted. "These findings highlight the importance of ocular screening among stroke patients and potential common pathogeneses underlying these conditions." ◀

Li HY, Yang Q, Dong L, et al. Visual impairment and major eye diseases in stroke: a national cross-sectional study. Eye. September 21, 2022. [Epub ahead of print].

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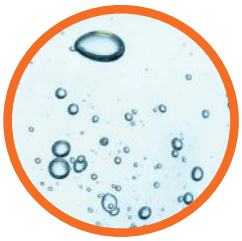

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helps protect against tear evaporation[11] to lock in moisture[5-8]

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

References: 1. Wasmanski AD and Kislan T. Cross-Over Evaluation of Polyethylene Glycol 400 (PEG-400) 0.4% and 0.25% Artificial Tears in Mild Dry Eye Patients. Invest. Ophthalmol. Vis. Sci. 2010;51(13):6263. 2. Montani G. Intrasubject Tear Osmolarity Changes with Two Different Types of Eye Drops. Optom. Vis. Sci. 2013;90(4): 372-377. doi: 10.1097/OPX.0b013e318288bdbe 3. Laurent TC. Structure of Hyaluronic Acid. In: EA Balazs (Ed.), Chemistry and Molecular Biology of Intracellular Matrix. Academic Press, London. 1970:703-732. 4. Aragona P, Papa V, Micali A, et al. Long Term Treatment with Sodium Hyaluronate-Containing Artificial Tears Reduces Ocular Surface Damage in Patients with Dry Eye. Br. J. Ophthamol. 2002;86(2):181-184. doi: 10.1136/bjo.86.2.181. 5. Prabhasawat P, Tesavibul N, Kasetsuwan K. Performance Profile of Sodium Hyaluronate in Patients with Lipid Tear Deficiency: Randomised, Double-Blind, Controlled, Exploratory Study. Br. J. Ophthalmol. 2007;91(1):47-50. doi: 10.1136/bjo.2006.097691. 6. Zheng X, Goto T, Shiraishi A, et al. In vitro efficacy of ocular surface lubricants against dehydration. Invest. Ophthalmol. Vis. Sci. 2013;32(9):1260-1264. doi: 10.1097/j.ico.0b013e31829cfd44. 7. Maissa C, Guillon M, Simmons P, et al. Effect of castor oil emulsion eyedrops on tear film composition and stability. Contact Lens Anterior Eye. 2010;33(2):76-82. doi: 10.1016/j.clae.2009.10.005. 8. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. The Ocular Surface. 2017;15(3):276-283. 9. US Dry Eye OTC Product Comparison. 10. IRI US 2020 Dry Eye Share Competitive Report. 11. JJV Data on File 2020. Blink Triple Care Lubricating Eye Drops - Consolidated, Approved Claims List. 12. 2012. Lemp, Miachael A. Distribution of Aqueous-Deficient and Evaporative Dry Eye in a Clinic-Based Patient Cohort: A Retrospective Study

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REVIEW of OPHTHALMOLOGY

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WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Necessity Can Be a Mother

The aphorism "Necessity is the mother of invention" doesn't really communicate how dire someone's need can actually be to prompt the ingenious creation of a solution. Many times, things are turning bad, the going is getting rough and your back is against the wall, and this pushes you to find a new way of doing things.

Though the matter isn't settled, and skeptics will provide well-reasoned objections to the practice of in-office cataract and retina surgery, many proponents of the new surgical approach turned to it as a response to forces that seemed bent on making their surgical lives tougher.

In our cover story on office-based surgery (beginning on p. 48), surgeons who've chosen to construct surgical suites in their offices tell stories of working in hospital and ambulatory surgery centers' operating rooms in which they have no control over which equipment they're going to use for a cataract case, nurses who can't identify which ophthalmic instrument is which and staff who can't locate key pieces of equipment at crucial times.

The retina community seems to almost have it worse than the cataract surgeons. (Pro tip: Don't have a retinal detachment if you can help it.) When faced with an emergency retinal detachment, they have to call around and beg hospitals and ambulatory surgery centers on the phone for operating room time as if they're making some kind of outrageous imposition. Meanwhile, the detachment patient is having an existential crisis as his condition potentially worsens.

Considering what we as consumers pay for our health care, learning what these poor detachment patients and their surgeons have to go through is embarrassing and enraging. In hearing their tales, you can see the necessity that pushes them to give an in-office surgery suite a go.

This theme of adapting to changing circumstances continues in our feature on interpreting the images generated by optical coherence tomographers (p. 58). With every new technology comes new challenges in working with it, such as the artifacts that can obscure images and confuse OCT users. Surgeons, however, have adapted. Here, they share their ways of dealing with these artifacts when they occur.

In an event more revolution than evolution, I wanted to announce the well-earned retirement of our Medicare Q&A section editor, Paul Larson, MBA, MMSc, COMT. For the past five years, Paul has helped our readers understand the sometimes mystifying world of Medicare coding, covering everything from cataract surgery to dry-eye management. We want to thank Paul for all his hard work, and wish him the best as he embarks on this new chapter of his life!

Taking the reins of the column will be Paul's colleague at the Corcoran Consulting Group, Mary Pat Johnson, COMT, CPC, COE. Welcome, Mary Pat! Both the staff and the readers of *Review* are looking forward to learning a lot from you.

— Walter Bethke
Editor in Chief

For the treatment of all stages of neurotrophic keratitis (NK)

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

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

Important Safety Information

WARNINGS AND PRECAUTIONS

Use with Contact Lens

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

Eye Discomfort

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

ADVERSE REACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Lactation

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

Pediatric Use

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

INDICATION

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

DOSAGE AND ADMINISTRATION

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

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

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

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

See more clinical data
OXERVATE.com/hcp

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

General Dosing Information

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

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

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

Recommended Dosage and Dose Administration

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

WARNINGS AND PRECAUTIONS

Use with Contact Lens

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

Eye Discomfort

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

ADVERSE REACTIONS

Clinical Studies Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

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

Impairment of fertility

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

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

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Blockchain 101 for Ophthalmologists

Experts discuss this disruptive technology and its potential uses in ophthalmology.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

In the popular news media, blockchain is often discussed in relation to cryptocurrencies or touted as a cure-all for anything and everything related to data. While a major player in the finance sector now, blockchain in health care is still in its infancy. Yet proponents say it has the potential to aid clinical research, help prevent counterfeit drugs and bolster health data security. You may begin to hear more about this technology in the coming years—both fact and fancy—so we spoke with experts to learn what blockchain is and how it could contribute to ophthalmology.

What Is Blockchain?

Blockchain is a form of distributed ledger technology designed to engender trust through transparency, common access and unalterable data structures. "Transactions are recorded in 'blocks' which are cryptographically linked to the previous block using that block's hash key, a type of unique identifier," explains Daniel Shu Wei Ting, MD, an associate professor at the Duke-National University of Singapore Medical School, director of the Singapore Health Service's AI Program and an ophthalmologist at the Singapore National Eye Centre, Singapore Eye Research Institute. "Every block is verified and approved by the blockchain's participants through a consensus mechanism before it's stored on the blockchain."

In the world of finance and cryptocurrency, where blockchain has already found a foothold, it's used to record transactions across many devices, including who owns currency, where it's located and how it was spent over time. In health care, blockchains will help to manage and transport large amounts of medical data.

"Help" is the key word here, according to Tim Mackey, MAS, PhD, a professor at UC San Diego in the Global Health Program and director of the Global Health and Data Policy Institute. "You never start off with blockchain as a solution," he says. "There's a lot of hype around blockchain, especially in the nonfungible token (NFT) market. We have to get around this idea that blockchain can solve everything and think of it more as just another facilitating technology that can enable trust in other systems."

Blockchain networks must have the following four characteristics:[1]

Blockchain is a form of distributed ledger technology that promotes trust through transparency and immutable data records. Experts say the technology could be used to safely transport patient data between various medical centers and labs, facilitate artificial intelligence development audits and aid clinical research by helping to identify potential participants and secure their data. *(Images courtesy of Getty Images.)*

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.

EVALUATING BLOCKCHAIN PROJECTS

What are some ways to tell whether a blockchain proposal is more hype than practical? Tim Mackey, MAS, PhD, a professor at UC San Diego in the Global Health Program and director of the Global Health and Data Policy Institute, says he considers these three things when evaluating a blockchain project:

1. Good architecture. "We generally look for a correct architecture that's fit for the purpose of the particular health-care problem," Dr. Mackey says. "For example, if it's a problem that relates to health-care records, what's the structure? Private? Public? Hybrid? What's the permission structure setup? What's the consensus mechanism? Does it have a smart contract layer? Does it address a particular need?"

2. A diverse team. "We often look for teams that have both health-care people and engineers, not just one or the other," he says. "We make sure there are people who understand what a blockchain can do, as well as understand the health-care angle."

3. Boring is often better. "The most boring use cases tend to be the best ones, e.g., enabling better chargebacks or resalable returns for items," he says. "In pharmaceuticals, when pharmaceutical products are sold to someone and then they're brought back into inventory, blockchain would ensure you could track them so they could be resold again. Those types of use cases don't sound super exciting, but they're actually some of the best use cases."

—*CL*

1. Consensus. All parties must agree on a transaction's validity for it to be considered valid.

2. Provenance. Participants know where an asset came from and how its ownership changed over time.

3. Immutability. Transactions can't be tampered with once they've been recorded to the ledger. If there's a transaction error, a new transaction must be used to reverse the error, but both of these entries will remain visible as part of the record.

4. Finality. The ownership of an asset or completion of a transaction is recorded in one shared ledger.

Within blockchains, there are three types of architectures: private; public; and consortium. As you may guess, a private blockchain is akin to a private network, where the blockchain is held by a single authority. Public blockchains, such as those used for cryptocurrency, allow anyone access. Consortium blockchains are a hybrid of public and private blockchains and are permissioned through multiple authorities. Experts say private and consortium blockchains will be useful for health care's high-security needs.

Uptake & Adoption

How soon can we expect blockchain to come to health care and the biomedical space? It may take years, Dr. Mackey says. "Health care is a unique and complex industry, and it's highly regulated compared to industrial sectors," he explains. "According to the Gartner Hype Cycle, [a five-stage graphical representation of a technology's maturation and application] blockchain is at the 'Peak of Inflated Expectations' and it's likely moving into the 'Trough of Disillusionment,' though I'm not sure I'd follow this curve as much for the health-care space.

"Much of blockchain adoption in health care will be centered on its money-saving potential," he continues. "By keeping more transactions trustworthy and automating processes through smart contracts [coding programs that automatically self-execute the exchange of value once specific agreements are triggered],[2] blockchain could save money—if people want to use it. They may not want to. Prescription benefit managers and billing companies that process reimbursements, for example, are the types of entities that blockchain is supposedly going to disintermediate. That means we may not use them as much, because one party will be able to talk to another party directly, in a more trusted manner.

"Choosing the right business model is another consideration," he says. "Maybe consortium members—e.g., multiple health-care systems—all want to address CMS auditing or record validation. Maybe they all pay a membership fee and then some governance authority operates a blockchain on their behalf. In that case, every party might share in the cost of the overall blockchain environment and pay a transaction cost as a membership fee.

"Consortium blockchains are prime candidates for health care, but getting all of the different consortium members to agree to the same governance principles is actually very hard," Dr. Mackey adds. "That's another thing that can slow adoption."

He says there are still some fundamental unanswered questions about blockchain in health care too. For instance, we don't yet know how much it'll cost to deploy at a health-care scale, and there may be issues of interoperability, such as the degree to which blockchain can interact with different health systems. "We also don't know what the add-value is," he says. "What can blockchain do that other systems such as cloud computing can't already do with a permission structure?"

One early venture into health-care blockchain research comes from Mount Sinai, which launched the Center for Biomedical Blockchain Research in 2018 with the goal of leading Mount Sinai's blockchain odyssey. The CBB's aims are to

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TARPRE-DB-0042 8/22

Because of blockchain technology's immutable nature, experts say it could assist with some newer needs that have cropped up during and since the COVID-19 pandemic, including contact-tracing, health/vaccination passports, tracking COVID-19 testing, disease reporting and ensuring the vaccine supply chain remains free of counterfeit vaccines.

identify real-world use cases for blockchain, separate hope from hype, evaluate and build new applications, and partner with industry.

Patient Data

A medical blockchain evaluation study reported that blockchain networks can preserve and exchange patient data through hospitals, diagnostic laboratories, pharmacy firms and physicians.[3] The group also reported a potential for enhancing medical record analyses, handling deception in clinical trials and improving data efficiency and security in health care.

Managing electronic health records is another potential blockchain space. There are several blockchain-based EHR companies today, but in these instances, blockchain is used to manage permissions and security, rather than serve as a repository for patient records. "There's no time in the immediate future where blockchain would replace EHRs," Dr. Mackey assures. "There are all sorts of challenges associated with putting EHR data on a blockchain. For example, storing patient records on blockchain may run into issues with HIPAA since it's a distributed ledger."

Nevertheless, the next step in patient-centric care will require decentralized, encrypted data, Dr. Ting says. "Medical data, especially in the era of telehealth and the Medical Internet of Things,[4] will need to be traceable and secure," he says. "Traditional health-care databases are centrally managed, and that opens them up to vulnerability and limits the extent and efficiency of data exchange. The COVID-19 pandemic also prompted a space for blockchain. The technology could be used to assist with contact-tracing and immutable health passports,[5] as well as keeping track of COVID-19 testing, disease reporting, and vaccine supply chain and distribution management."

Health Insurance Claims

An estimated $2.6 billion loss in the United States is attributed to health-care fraud and abuse.[6] Experts say blockchain may be able to improve patient, hospital and insurance provider communication, prevent duplicate claims and eliminate the multiple rounds of review required for claims approval.

Notably, in the insurance claim submission and reimbursement process, the patient isn't included, Dr. Mackey points out. "This opens up the risk of fraud, but blockchain could mitigate that through secure data management and transparency," he says. His group created a prototype blockchain framework to record claims data and transactions in an immutable format so that the patient could participate as a validating node in their insurance coverage.[6] The prototype included consensus algorithms, smart contracts, tokens and governance based on digital identification on Ethereum, a blockchain-powered platform. They reported that their proposed framework would make the claims adjudication process more patient-centric and help to identify and prevent fraud and abuse.

"Theoretically, blockchain creates an auditable data log agreed upon by the parties," Dr. Mackey says. "CMS audits are one use case for blockchain. If everyone has agreed to a record being written to the blockchain, and it's validated across multiple parties, and it's transparent, then you wouldn't necessarily have to go through a full process of an audit to look for those documents and try to validate billing.

"Now, a lot of times the people authorizing or validating that information aren't CMS or a payer, but a payer could come and look at that information," he continues. "On a blockchain, it can't be changed and it's cryptographically hashed. As long as the parties were in good faith, then you have a record that's much more trustworthy than, say, public records. In our paper, we proposed that the patient come in and also validate the insurance information, so if there's fraud, the patient would be able to verify whether they got the medical equipment or the prescription that was prescribed. You can do additional validation by adding notes to the blockchain."

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ENVIRONMENTAL IMPACT

"A lot of people talk about the environmental impact of Bitcoin because it uses a consensus algorithm that's called Proof of Work," says Tim Mackey, MAS, PhD, a professor at UC San Diego in the Global Health Program and director of the Global Health and Data Policy Institute. "Essentially, this requires a lot of machines to randomly solve problems, and users mine Bitcoin by solving these random mathematical problems.

"However," he continues, "in most business blockchains, you wouldn't adopt a Proof-of-Work algorithm. So, if you use a different type of consensus mechanism, the computing power required to do that would probably not be any more than that of cloud computing or anything like that, depending on your type of consensus. There are other much simpler ways of doing consensus.

"Much of the environmental impact concern relates to cryptocurrencies and financial technologies like FinTech," he continues. "There are environmental impacts because of the computing time it takes, but those things can be mitigated to a certain extent with just a different design of a blockchain."

—*CL*

tracks a product across multiple parties, and everyone involved has a single source of information they can trust about where the product was shipped to and from, and so on," Dr. Mackey says.

As you may recall, in February 2012, the American Society of Retina Specialists was notified by Genentech that a counterfeit drug labeled as Avastin had been distributed in the United States by a foreign supplier. Vials of the counterfeit drug had been found in oncology practices in the United States. In the following years, the FDA issued more than 1,000 warning letters to physicians and medical practices as more counterfeit batches were discovered.[7]

An outbreak of intraocular inflammation later found to have been caused by endotoxin-contaminated counterfeit bevacizumab was reported in China in 2013.[8] In 2015, ophthalmologists reported 15 cases of intraocular inflammation following injections of counterfeit bevacizumab in Gujarat, India.

The counterfeit drug problem is a very complex social, economic and public-health issue.

While not a solution in and of itself, blockchain has the potential to shore up the supply chain against counterfeits by acting as an architecture for sharing and validating trustworthy data across multiple parties.

"The pharmaceutical supply chain has many actors," Dr. Mackey explains. "We'd like to validate data that's coming from those different actors and identify where there's a potential for drug diversion or drug counterfeiting. In a traditional supply-chain model, we could have all of these different parties feeding information into the blockchain. If the parties don't agree that a trader is providing legitimate information, then that anomaly can be detected quickly. Because of shared information and visibility, blockchain could support much earlier identification of exploitation.

"But when it comes to counterfeit Avastin, there were illegitimate supply chain actors such as online pharmacies or unregistered distributors," he continues. "It may be harder to detect these types of actors since they're outside of the controlled supply chain. The Drug Supply Chain Security Act is in place in the United States now, and it requires track-and-trace across the whole supply chain. Blockchain has been explored as one potential technology that could facilitate better implementation of the DSCSA, but it's not the only one. It's an additive technology. We'll still need technology that's able to detect counterfeits and test them quantitatively through analytical chemistry. We'll need barcodes and other anti-counterfeiting packaging approaches."

Clinical Trials

There are several blockchain use cases for clinical trials. Blockchain may make it easier to obtain participant consent and to update consent protocols, for example. "You could use blockchain to recruit patients based upon validated information about their health status and to better match patients to trials regarding inclusion and exclusion criteria," Dr. Mackey says. "It may expand the pool of potential clinical trial candidates. It may also help to coordinate the different parties involved in clinical trials—whether it be data monitoring, data safety, the board, study sites, the investigators—they'll all have the validated ledger of every transaction going on.

"As I noted before, blockchain may disintermediate aspects such as a clinical research organization that currently manages many of these processes," he says. "There may be less work with blockchain and smart contracts automating some of these processes. We could also have more decentralized or distributed trials—e.g., trials done in a home care setting, not at the site itself. Blockchain would help to validate the information from all those different sources."

Remote Monitoring

More and more companies are developing remote-monitoring technology, from at-home OCT and IOP monitoring to the many types of wearable tech from giants such as Apple, Google and Samsung. "Blockchain can aggregate and validate data across multiple sources, and that has a lot of potential for decentralized clinical trials," Dr. Mackey says.

"Many patients want to access and have ownership over their health data, and potentially share it with

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IMPORTANT PRODUCT INFORMATION

CAUTION: Federal law restricts this device to sale by or on the order of a physician. INDICATIONS FOR USE: The Hydrus Microstent is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG). **CONTRAINDICATIONS:** The Hydrus Microstent is contraindicated under the following circumstances or conditions: (1) In eyes with angle closure glaucoma; and (2) In eyes with traumatic, malignant, uveitic, or neovascular glaucoma or discernible congenital anomalies of the anterior chamber (AC) angle. **WARNINGS:** Clear media for adequate visualization is required. Conditions such as corneal haze, corneal opacity or other conditions may inhibit gonioscopic view of the intended implant location. Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, peripheral anterior synechiae (PAS), angle closure, rubeosis and any other angle abnormalities that could lead to improper placement of the stent and pose a hazard. The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. The surgeon should periodically monitor the status of the microstent with gonioscopy to assess for the development of PAS, obstruction of the inlet, migration, or device-iris or device-cornea touch. The Hydrus Microstent is intended for implantation in conjunction with cataract surgery, which may impact corneal health. Therefore, caution is indicated in eyes with evidence of corneal compromise or with risk factors for corneal compromise following cataract surgery. Prior to implantation, patients with history of allergic reactions to nitinol, nickel or titanium should be counseled on the materials contained in the device, as well as potential for allergy/hypersensitivity to these materials. **PRECAUTIONS:** If excessive resistance is encountered during the insertion of the microstent at any time during the procedure, discontinue use of the device. The safety and effectiveness of use of more than a single Hydrus Microstent has not been established. The safety and effectiveness of the Hydrus Microstent has not been established as an alternative to the primary treatment of glaucoma with medications, in patients 21 years or younger, eyes with significant prior trauma, eyes with abnormal anterior segment, eyes with chronic inflammation, eyes with glaucoma associated with vascular disorders, eyes with preexisting pseudophakia, eyes with pseudoexfoliative or pigmentary glaucoma, and when implantation is without concomitant cataract surgery with IOL implantation. Please see a complete list of Precautions in the Instructions for use. **ADVERSE EVENTS:** The most frequently reported finding in the randomized pivotal trial was peripheral anterior synechiae (PAS), with the cumulative rate at 5 years (14.6% vs 3.7% for cataract surgery alone). Other Hydrus postoperative adverse events reported at 5 years included partial or complete device obstruction (8.4%) and device malposition (1.4%). Additionally, there were no new reports of persistent anterior uveitis (2/369, 0.5% at 2 years) from 2 to 5 years postoperative. There were no reports of explanted Hydrus implants over the 5-year follow-up. For additional adverse event information, please refer to the Instructions for Use. **MRI INFORMATION:** The Hydrus Microstent is MR-Conditional meaning that the device is safe for use in a specified MR environment under specified conditions. **Please see the Instructions for Use for complete product information.**

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2. Hydrus Microstent Instructions for Use

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> **We have to get around this idea that blockchain can solve everything and think of it more as just another facilitating technology that can enable trust in other systems.**
>
> ***— Tim Mackey, PhD***

other parties outside the closed software systems," he continues. "Many of these remote patient monitoring devices collect data for clinical trials, but the portability of that data still isn't there. That portability could potentially be facilitated by blockchain or a digital wallet."

Artificial Intelligence

Artificial intelligence is poised to shape the future of health care, but it's somewhat limited by a lack of access to data. "Data privacy laws such as HIPAA and the General Data Protection Regulation prevent proper data sharing and make global collaboration difficult," Dr. Ting says. "Data could be managed through smart contracts and node authentication. Additionally, privacy-preserving processes such as federated learning could facilitate peer-to-peer sharing."

Transparency in the development process is another concern that blockchain could address. Dr. Ting says he sometimes has difficulty verifying AI papers he receives as a journal editor because he's unable to access the original dataset or because some of the development details are in the black box. By preserving each step of development immutably on the blockchain, he says auditing and verifying AI development would be simpler and more transparent.

The Future Landscape

Though it's a disruptive technology, Dr. Mackey says the impact of blockchain on your clinical practice is something you won't see. "Hopefully, a lot of the blockchain technology we're talking about will operate in the background," he says. "There may also be a wave of consumer health applications that are blockchain-based, where people generate their own health information from wearables and other consumer health information sources. Genomic data is now available to the consumer too, with direct-to-consumer testing.

"So, what you may see in the future is a bifurcation of the market: the clinical blockchain applications you'll never see that just make things run smoother, versus the consumer health applications," he concludes. "Blockchain applications could give patients more access to their own data, let them be more active in their health-care decisions and share that data actively or even potentially monetize it. We'll see how those two areas grow, but these are two likely spaces in health care where we'll see blockchain emerge."

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DISCLOSURES

Dr. Mackey is the owner of technology and health startup company S-3 Research, which is funded by a National Institutes of Health SBIR grant and uses digital ledger technology. **Dr. Ting** is the co-inventor of a deep-learning system for retinal disease.

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Be Afraid, Be Very Afraid

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

In last month's e-newsletter I briefly commented about the shaky financial premise of cataract surgery, noting that, without income streams from such things as premium lenses or in-office services we lose money on every case.

This has been true for some of us for some time, and for others it's not far off. Why has payment for cataract surgery continued to decline? Is it cheaper to perform? No—and the associated costs of running a practice continue to increase. With balance-billing requirements we're the only service that can't pass on our costs to our "customers," so we've had to figure out how to compensate. And, yes, we can take home fewer dollars, but who wants to? Don't we deserve a raise or at least a cost-of-living adjustment? I suppose that depends on how well you think ophthalmologists have been paid—or perhaps overpaid—over the years. It's hard to generalize since there are so many local variances of practice type, different levels of overhead, etc. However, the general trend has been sobering and getting worse. We are running out of ways to pull rabbits out of our hats.

It's an established fact that we're victims of our own success, and maybe our hubris. We made cataract surgery so much faster, more predictable and more successful that it was easy for non-ophthalmologists to trivialize it. With the outcomes being this good and the procedure this safe, we drove the surgery's indications down to where almost anyone with lens changes could benefit. No one wanted their vision to be even a little bit blurry.

Over time—and, again, this isn't new—cataract surgery became the most frequently performed procedure in Medicare, by a lot. Of course, this made it the largest dollar outlay of the program. Or, as one might say, "Our butts were the highest and the driest." Cataract surgery was the perfect target when someone wanted to control costs.


Getty

So, what's changed? Nothing, except that we're running out of ways to lower our costs, improve our efficiency, and develop patient-pay add-ons—and the reimbursements will only continue to go lower. The next shoes to drop are more physician retirements and a further move to selling practices to private equity or academic centers. In other words: the death of private practice. Neither private equity nor academic institutions have a magic formula for making more money from cataract surgery. There's only so much more inefficiency to be wrung out of clinical care, and we're reaching the end of that. Academic centers have other lines of work and other sources of income, such as research monies, that can paper over the losses in clinical care—but, again, only to a point.

What I'm saying above applies not only to cataract surgery but to most of ophthalmology. Try making a living as a pediatric or neuro-ophthalmologist. Other subspecialties aren't far behind.

This brings us to the proverbial cliff: While we're suffering from declining reimbursements, the entities that pay us are completely unsustainable. The coming demographic changes ensure health-care Armageddon: an aging population; fewer people working; and for-profit insurance companies that answer to their shareholders, not their patients. Medicare part B, which pays for physician services, is supported directly from the federal budget, with only 15 percent coming from Medicare premiums. This means Congress needs to approve these monies every year, which is an almost impossible task given the increasing percentage of our GDP devoted to health care.

There are further reimbursement cuts on the way, and a push to totally revamp the physician pay program. You know that will mean even less money. And despite all this, we just keep rearranging the deck chairs … .

While few want to ration care, the current system of patient-driven utilization can't continue. Some new form of health-care delivery is inevitable, either by design or from the ashes of our pending cataclysm. I'd like to think we can do this rationally but given how messed up the public space is currently, that's not going to happen. Time to find a life raft. ◀

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

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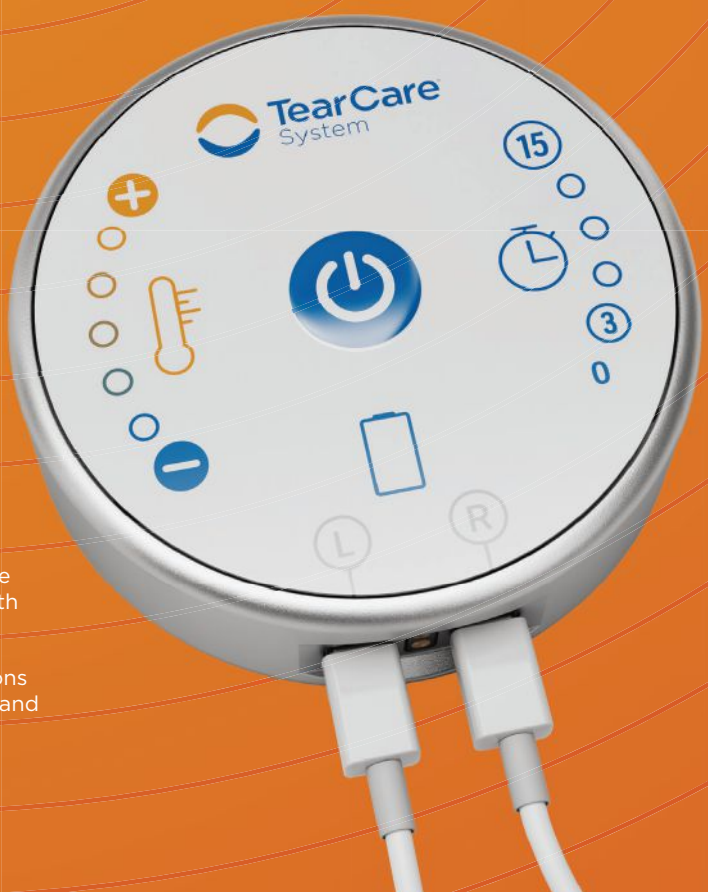

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Stop the 'Trainwrecks'

The right attitude and proper surgical planning can help you handle even the most difficult patients.

ARUN GULANI, MD
JACKSONVILLE, FLA.

When you're faced with a patient with a history of keratoconus and multiple failed surgical procedures, it can be easy to get discouraged when thinking of all the possible pitfalls and difficulties. One's inclination might be to advise the patient that nothing more can be done. I'm here to tell you that, with the right attitude and approach, you can help even the most difficult patient. In this article, I'll discuss how I approach difficult cases, personalities and situations, in theory and with some case examples.

Attitude & Empathy

More than 70 percent of my practice is seeing second opinions and unhappy patients with complications. I take them on despite their complexity, skepticism and demanding nature and strive to have the right attitude and empathy when treating them. For surgeons who ask about how to approach difficult cases, I tell them I don't differentiate between simple and complex cases; in my mind, every eye I operate on is precious, so I never let my guard down, from diagnosis to performance. You must be committed to safely taking each patient's eye to its best vision potential.

Have a Full Toolbox

To help me approach difficult cases, I've developed a surgical system called KLEAR (Full Spectrum Kerato-Lenticulo-Refractive surgeries). As the name implies, KLEAR involves a mélange of refractive, corneal and lens procedures, including staged and combined techniques. Since these patients' problems can have many "moving parts," properly planning the steps for them can be a challenge; in fact, KLEAR combines a group of personal surgery algorithms I've nicknamed the Gulani Planning System. This method takes a holistic approach to the visual system, individually tailored to each eye's particular problems.

For the procedures I plug into this algorithm as needed, I've developed a surgical approach called "Plastique," which is composed of "Corneoplastique" for cornea; "LaZrPlastique" for laser vision techniques and "LenzOplastique" for lens-based surgeries, including cataracts. Within Plastique is a mindset of a commitment to fight for each patient's best vision potential. This includes not just fixing the problem at a basic level (like repairing a broken leg and giving the patient a cane), but instead striving for actual improved visual function (instead of needing a cane, the patient can eventually go running after the surgery). I also try to do this in the least interventional and most aesthetically oriented way possible, allowing the patient to enjoy a comfortable surgical and post-surgical experience. This, of course, makes it a bigger challenge, and my work becomes more difficult. In the end, however, it's worth it.

Following are a sampling of cases that show my particular approach in action.

Case 1

This 74-year-old with keratoconus underwent premium cataract surgery, and his surgeon performed a YAG capsulotomy. The patient was left with hyperopia, presbyopia, an anterior superficial scar and high keratometry; he was miserable, because his vision was 20/200. This patient also happened to be a pilot.

Many excellent eye surgeons he consulted told him that his surgeon had made a mistake, that they would approach his case by first removing this "wrong" lens implant and then attaching a new, scleral-supported lens implant (stitched/glued/iris-supported, etc.) since the posterior capsule was open. Now, none of these able surgeons was wrong, but here's where my attitude and empathy differ (surgical acrobatics does not translate to vision artistry): Removing this lens implant and stitching a new lens implant with vitrectomy won't bring the patient to unaided 20/20 vision.

The patient was facing many vision issues: astigmatism, farsightedness, and central scarring. For all of these to be corrected, I needed to perform myopic laser surgery. However, he was hyperopic. Keeping the Plastique mindset of going the extra mile, my first thought was: How do I make him myopic?

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.

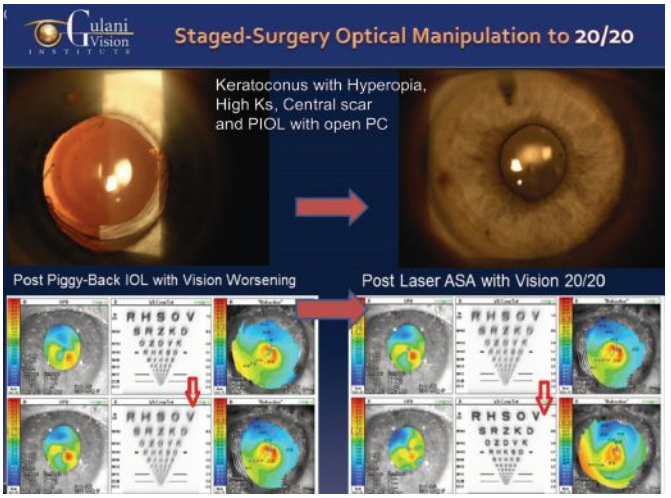

Figure 1. A 74-year-old with keratoconus presented with hyperopia, astigmatism and central scarring. *(See Case 1)* Dr. Gulani first made the patient myopic with a piggyback lens, followed by myopic refractive surgery six weeks later.

Because of his steep keratometry (due to keratoconus), he had a deep chamber, and he already had a lens in place (with open posterior capsule), so I put a piggyback lens in and made him myopic. He was then myopic with astigmatism, central scarring and high keratometry. Six weeks later, upon determining stability, I performed myopic laser refractive surgery. The patient ended up 20/20-plus uncorrected—he actually had 20/15 vision—and he got his pilot's license back.

This also shows the patient's trust, because I made him worse in the first stage in order to then move forward to my goal (keeping the two procedures minimally interventional, brief, painless, topical and aesthetically pleasing).

Case 2

An 80-year-old female patient presented with a history of hexagonal keratotomy, the opposite of radial keratotomy, performed nearly 30 years ago. As some may recall, with Hex-K, the surgeon makes hexagonal-shaped cuts on the cornea. Unfortunately, we now know that this procedure destabilizes the entire cornea and, as a result, this patient wound up with 23.5 D of irregular astigmatism and keratometry of 89 D. She also had cataract, Fuchs' dystrophy and thyroid exophthalmos. She was told nothing could be done except for corneal transplant and lens surgery.

My goal, however, was to get her to 20/20. Taking into account her vision issues and related anatomical challenges, I first implanted Intacs around the hexagonal cuts. I did this confidently, yet carefully; if I came too close to the center, I'd tear into the cuts and perforate the cornea and if I went too peripheral, I'd be hitting the sclera. Having successfully inserted both the rings to "hug" the destabilized, ectatic corneal area inside the hex cuts, and having achieved my titratable central circular corneal reflex, I immediately cross-linked the cornea to make this effect permanent.

Four months later, I confirmed corneal stability and measurability. The procedure brought the irregular astigmatism down from 23.5 D to 1.4 D. I proceeded with cataract surgery with a toric IOL implantation, and brought her vision to 20/25. Fortunately, these two surgeries were brief, painless and aesthetically pleasing, and she now has visual freedom.

Case 3

A 60-year-old male with keratoconus and a corneal scar came to me after 12 failed procedures. Among the 12 surgeries were Intacs, multiple corneal cross-linking procedures, PTK, PRK and ICL (the last being an example of a well-meaning surgeon who actually confuses the patient's optics).

The first step I did was LaZrPlastique on his corneal scar. This is a proprietary surface laser technique where I improve scars in a refractive mode. This removed his scar and made the cornea measurable. Because he also had a cataract and an ICL in the eye, I removed the ICL and the cataract, leaving him aphakic with an empty capsular bag (since I wasn't confident his corneal measurements were good enough for an accurate IOL implantation). I measured his refraction the next day (using the Mackool-Gulani modified aphakic refraction technique) and, a week later, with full confidence,

(Continued on page 35)

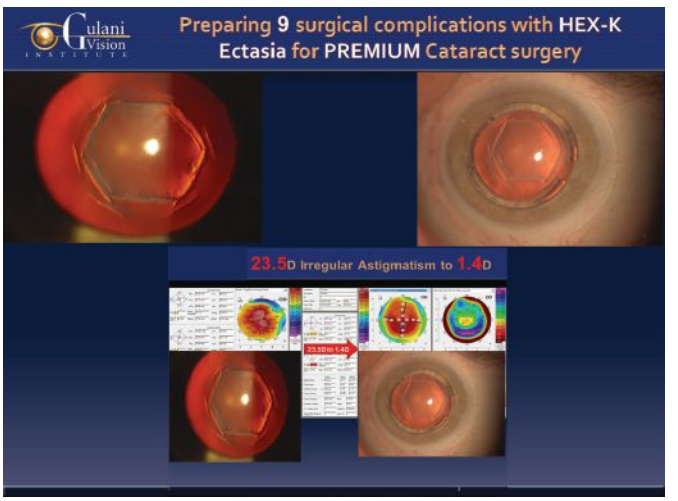

Figure 2. Patient with Hex-K and 23.5 D of irregular astigmatism *(Case 2)*, was brought to 1.4 D after Intacs surgery.

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- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

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EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

Demonstrated efficacy outcomes in VISTA and VIVID, phase 3 anti-VEGF trials in DME (N=862)[1]

Mean change in BCVA (ETDRS letters) at Year 1 from baseline[1-5,*]

	Initial Gains (Month 5)		Primary Endpoint (Year 1)		Prespecified Exploratory Endpoint (Year 3)	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
EYLEA Q4	+10.3 (n=154)	+9.3 (n=136)	+12.5 (n=154)	+10.5 (n=136)	+10.4 (n=154)	+10.3 (n=136)
EYLEA Q8†	+9.9 (n=151)	+9.3 (n=135)	+10.7 (n=151)	+10.7 (n=135)	+10.5 (n=151)	+11.7 (n=135)
Control	+1.8 (n=154)	+1.8 (n=132)	+0.2 (n=154)	+1.2 (n=132)	+1.4 (n=154)	+1.6 (n=132)

P<0.01 vs control at Year 1.

The analyses of these exploratory endpoints were not multiplicity protected and are descriptive only.

Year 2 data was consistent with results seen in Year 1.[5]

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled clinical studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received: 1) EYLEA 2 mg Q8 following 5 initial monthly doses; 2) EYLEA 2 mg Q4; or 3) macular laser photocoagulation (control) at baseline and then as needed. From Week 100, laser control patients who had not received EYLEA rescue treatment received EYLEA as needed per re-treatment criteria. Protocol-specified visits occurred every 28 (±7) days.[1]

In both clinical studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52, as measured by ETDRS letter score.[1]

*Last observation carried forward; full analysis set.
†Following 5 initial monthly doses.

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- 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.** Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology.* 2014;121(11):2247-2254. doi:10.1016/j.ophtha.2014.05.006 **3.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **4.** Data on file. Regeneron Pharmaceuticals, Inc. **5.** Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. *Ophthalmology.* 2016;123(11):2376-2385. doi:10.1016/j.ophtha.2016.07.032

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

04/2021
EYL.21.03.0211

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
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Tarrytown, NY 10591

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Initial U.S. Approval: 2011

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

EYL.20.09.0052

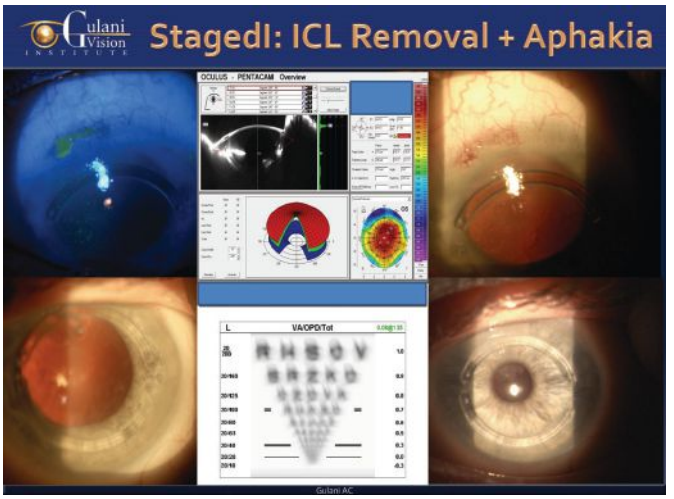


Figure 3. After 12 failed procedures, this patient with keratoconus came to Dr. Gulani, who performed LaZrPlastique to remove his corneal scar, followed by removal of his cataract and ICL and implanting a toric IOL. *(Case 3)*

(Continued from p. 31)

Stop the 'Trainwrecks'

implanted a toric IOL. This brought him to 20/20 uncorrected.

Case 4

This next case shows how my thought process works. A 60-year-old man traveled to me with a history of radial keratotomy and a corneal transplant. He had since developed a cataract and also had high irregular astigmatism of 8 D and 20/200 vision. With this combination of procedures in his history, surgeons were hesitant to treat him any further.

However, it's important to not let the difficulty level change your mindset about the patient. Fortunately, his cornea, no matter how astigmatic it was, was at least measurable. I went straight inside the eye and worked on the cataract and got him to 20/25. I did this through my LenzOplastique method in which I don't just think about the cataract, I use cataract surgery as a vehicle to manipulate the optics and cancel the corneal abnormality. His postop topographical astigmatism was still around 8 D, but he could see 20/25 unaided and was thrilled with his outcome.

Case 5

This next case was a surgeon himself, with a history of a 20+ cut RK, a full-thickness, central blinding scar, more than 15 D of irregular astigmatism and cataracts. Vision was 20/400 uncorrected. And here's the "best" part: Both eyes had this same complexity.

His team of ophthalmologists referred him to me. Even though his cornea was completely unmeasurable, I still didn't want to do a full transplant and deprive him of his active lifestyle as a surgeon and golfer, so I performed my Corneoplastique-based, manual lamellar keratoplasty through the intersecting RK cuts to remove just the top layer of the scar. I then implanted a lamellar donor cornea without going inside the eye. Seventeen months later, I performed sutureless cataract surgery using a toric premium lens implant (LenzOplastique; lens-based surgery to optically cancel corneal anatomical complexities). As always, despite the complexities, I used only topical anesthesia without a sedative, and he saw 20/25. With the lamellar technique, the astigmatism went from 15.1 to 1.9 D, and the toric IOL treated the remaining cylinder. I repeated the same approach for the second eye, with similar results.

Case 6

This 73-year-old female was referred to us with poor visual outcomes following premium cataract surgery with multifocal lens implant followed by YAG laser capsulotomy. Her surgeon, in an effort to correct the hyperopic surprise, performed multiple PRK surgeries and caused a corneal scar. She was relegated to a corneal transplant with lens implant exchange along with vitrectomy by many surgeons she consulted. When she arrived I noted her vision issues and planned my least interventional, yet still "Plastique," approach.

I first proceeded with LaZrPlastique to refractively clear the corneal scar to make the cornea measurable and stable. We then implanted a piggyback IOL in the same eye using LenzOplastique principles, which resulted in a 20/25 visual outcome.

These everyday cases at our institute are examples of how having a spectrum of techniques and technologies and, more importantly, a good attitude and empathy for each and every patient, enables you to handle the most complex refractive, corneal and premium cataract surgical failures or complications. Even if you have to go in reverse first, and then sideways, you'll eventually end up going forward and enhancing the patient's outcomes. Don't be apprehensive about stepping out of your comfort zone and only doing things "by the book." Also, don't focus on surgical acrobatics that deprive patients of 20/20 unaided vision. I have numerous patients flying to me, disgruntled that their surgeons were happy with a smooth topography, clear corneal transplant or well-centered secondary lens implant while the patient was suffering from less-than-optimal vision.

To use a metaphor from the culinary world: Focus on the "vision recipe," not just one ingredient (lens implant). I want my colleagues to use their ingredients, tools and recipes to take every patient—from the simple to the complex—to great vision and become master chefs. ◀

ABOUT THE AUTHOR

Dr. Gulani is the founder of Gulani Vision Institute in Jacksonville.

NOT A DRY EYE IN THE HOUSE: LATEST TREATMENTS

Clinicians share how they approach this complex ocular surface condition and the treatments they use.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

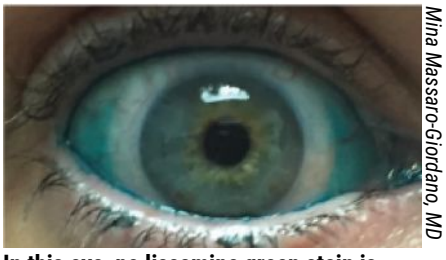
Dry eye's effects on quality of life and vision are more widely recognized today, especially in the refractive cataract surgery space, where an optimized ocular surface is vital for obtaining accurate corneal measurements. There are an abundance of dry-eye treatment options, with more advances coming down the pipeline each day. Nevertheless, the condition remains challenging to treat due to its multifactorial nature and often conflicting signs and symptoms. Here, experts discuss their treatment strategies for the many faces of dry eye.

Redefining the Disease

Experts note that dry eye's range of clinical presentations and symptoms has made it a challenge to define, and the lack of standardized terminology has hindered the strength of research. "Patients with dry eye don't necessarily have dry eyes," points out Mina Massaro-Giordano, MD, co-director of the University of Pennsylvania's Dry Eye and Ocular Surface Center in Philadelphia. "There are multiple causes for ocular surface disease. The challenge is homing in on the right ones to tailor your treatment, which requires constant monitoring and management, usually with more than one medication."

There have been several definitions and diagnostic criteria for DED over the years, including those proposed by the National Eye Institute, the Tear Film & Ocular Surface Society Dry Eye Workshops I and II, the Japanese Dry Eye Research Group, the Korean Corneal Disease Study group, the Asia Dry Eye Society, and the American Academy of Ophthalmology.

The most recent definition, published in the *International Journal of Molecular Sciences* in 2020, was drafted with the clinician in mind by a group of global DED experts who convened at four meetings between 2016 and 2018. Their consensus definition states: "Dry eye is a multifactorial disease characterized by a persistently unstable and/or deficient tear film causing discomfort and/or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation and neurosensory abnormalities."[1]



Mina Massaro-Giordano, MD

In this eye, no lissamine green stain is visible under the area covered by the scleral lens.

Stephen C. Pflugfelder, MD, of Houston's Baylor College of Medicine, says the new definition is meant to be clinically applicable and to promote consistent diagnoses. "The group felt that dry eye is really a disease defined by an unstable tear film," he explained. "Tear dysfunction is easy to measure in the clinic, making it a practical and reproducible marker of DED. Once tear-film instability has been identified, additional testing can be done to identify

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Dr. Christenbury is a speaker for BioTissue. **Dr. Pflugfelder** is a consultant for AbbVie, Dompé, Kala Pharmaceuticals, Aerie, Allergan and Kowa. **Dr. Massaro-Giordano** is a consultant for Oyster Point, Kala, Physician Recommended Nutriceuticals, Clarus and Dompé. **Dr. Armstrong** has no related financial disclosures.

TABLE 1. SOME TEAR REPLACEMENT THERAPIES

iVizia	Similasan	A preservative-free artificial tear with sodium hyaluronate, polymers and trehalose. Available in multidose bottles. Lubricant eye gel available in single-dose vials.
Clear Eyes Pure Relief	Prestige Consumer Healthcare	A preservative-free artificial tear formulated with glycerin and sodium hyaluronate. Available in multidose bottles.
Optase Dry Eye Intense	Scope	A preservative-free artificial tear with hyaluronic acid. The MGD Advanced lipid-based drop is also preservative-free. Both are available in multidose bottles.
Biotrue	Bausch + Lomb	A preservative-free artificial tear with hyaluronic acid. Available in single-dose vials and multidose bottles. Safe to use with contact lenses.
Blink Triple Care	J&J Vision	A hypo-osmolar viscoelastic formula that mimics human tears to restore the tear film and provide relief from dry-eye symptoms by regulating osmolarity levels.
Retain HPMC	Ocusoft	A hypromellose ophthalmic solution 0.3% that relieves dry-eye symptoms by resembling natural tears.
Freshkote	Eyevance	Supports the eye's tear film with antimicrobials and a blend of polyvinyl alcohol 2.7% and povidone 2%, which results in high oncotic pressure on the ocular surface to draw excess water from epithelial cells. Preservative-free.
Systane Hydration	Alcon	A preservative-free artificial tear formulated for sensitive eyes with HydroBoost. Available in multidose bottles.
Soothe XP Emollient	Bausch + Lomb	Restores the lipid layers with mineral oils to seal in moisture and protect against irritation.
Refresh Optive Mega-3	Allergan	Restores the lipid layer with a natural oil blend and relieves MGD symptoms. Includes carboxymethylcellulose sodium 0.5%, glycerin 1% and polysorbate 80 0.5%. Preservative-free.
Refresh Celluvisc	Allergan	A preservative-free artificial tear gel that contains carboxymethylcellulose sodium 1%.
TheraTears	TheraTears	A hypotonic, electrolyte-balanced formula that replicates healthy tears.

the underlying cause of the dry eye, such as inflammation levels or other factors associated with an unstable tear film."

Mild Dry Eye

Clinicians say almost any artificial tear available over the counter will effectively alleviate some mild dry-eye symptoms. "I don't make a big distinction among the different brands, but I may recommend a tear with a lipid-based component, for example, if there's a meibomian gland problem," says Grayson W. Armstrong, MD, MPH, of the Massachusetts Eye and Ear Infirmary. "I tell my patients they'll probably be fine with any OTC tear. I'll push them to use preservative-free options if they're going to be using drops frequently (e.g., more than four times per day)."

"There haven't been many head-to-head comparisons of various artificial tears, but certain components may give some formulas an edge over others," Dr. Pflugfelder says. "Personally, I prefer artificial tears that contain hyaluronic acid. There are a number of those in the United States [e.g., Blink Tears (Johnson & Johnson Vision) and Systane Hydration PF (Alcon)]. Hyaluronic acid tends to lubricate and retain tears better because it binds moisture to the eye and reduces surface friction. There are also tears with osmoprotectants in them such as glycerin, erythritol and carnitine, which may decrease inflammation and protect the eye from high osmolarity."

Proactive artificial tear use goes a long way toward providing symptom relief. In addition to using tears throughout the day, if necessary, Dr. Armstrong specifically encourages his patients to instill tears before they plan to read, look at their phone or do computer work for long periods of time. "Many of my patients tell me their dry eye is worse in the evening, which also happens to be when they read," he says. "Using drops prophylactically, remembering to blink and taking breaks every 20 minutes is sometimes enough for cases of mild dry eye."

Though artificial tears are a mainstay of DED care, experts note that they're not always appropriate for every patient as a first-line option. "In general, I find that patients are pretty noncompliant with artificial tears," Dr. Armstrong says. "I try to recommend a treatment that makes sense for the patient's compliance level. Sometimes I'll recommend warm compresses or lid scrubs first if the patient has a meibomian gland or blepharitis problem. In Massachusetts, we have a cold climate, and heaters dry out patients' homes, so I'll often suggest using a humidifier as well."

Making small environmental or behavioral changes can alleviate some mild dry-eye symptoms, Dr. Pflugfelder points out. For mild "level-one" cases, he also often recommends humidifiers and other modifications such as avoiding drafts or positioning the video display at eye level. "It depends on patient preference," he says. "If they don't respond to these measures, or to artificial tears, I often introduce an

TABLE 2. SOME OPTIONS FOR TREATING INFLAMMATION, PROMOTING TEAR PRODUCTION AND/OR RESTORING THE OCULAR SURFACE

Tyrvaya	Oyster Point	A prescription varenicline solution nasal spray that stimulates the trigeminal nerve to naturally increase tear production.
Restasis	Allergan	A prescription ophthalmic emulsion (cyclosporine 0.05%) that increases the eye's natural ability to produce tears and reduces inflammation.
Generic cyclosporine ophthalmic emulsion 0.05%	Mylan Pharmaceuticals	The first FDA-approved Restasis generic (cyclosporine ophthalmic emulsion 0.05%), available in single-use vials.
Cequa	Sun Ophthalmics	A cyclosporine ophthalmic solution 0.09%; this prescription drop increases tear production using nanomicellar technology.
Xiidra	Novartis	A prescription drop (lifitegrast ophthalmic solution 5%) that targets the source of dry-eye inflammation.
Lotemax	Bausch + Lomb	A loteprednol etabonate ophthalmic suspension 0.5% often used off-label for treating dry eye.
Inveltys	Kala Pharmaceuticals	A loteprednol etabonate ophthalmic suspension 1% with mucus-barrier penetration technology, often used off-label for treating dry eye.
Eysuvis	Kala Pharmaceuticals	A loteprednol etabonate ophthalmic suspension 0.25% with mucus-barrier penetration technology for dry eye.
Klarity-L Drops	ImprimixRx	A preservative-free loteprednol-chondroitin 0.5% ophthalmic suspension for controlling acute inflammation.
Klarity-C Drops	ImprimisRx	A preservative-free cyclosporine ophthalmic emulsion 0.1%.
Oxervate	Dompe	A cenegermin-bkbj ophthalmic solution 0.02% (recombinant human nerve growth factor) for treating neurotrophic keratitis. Currently in Phase II trials for dry eye (rhNGF 20 µm/ml).
iTear100	Olympic Ophthalmics	A handheld, noninvasive neurostimulator that stimulates the trigeminal nerve to increase tear production.

anti-inflammatory therapy."

For patients with aqueous deficiency, punctal plugs may also provide some relief. "I start with dissolvable plugs (three- or six-month duration) because I'm not sure the patient will like them," Dr. Pflugfelder says. "Non-dissolvable plugs are usually made of silicone, and they have a mushroom shape, so there's a portion of the plug that comes out to rest on top of the punctum. Sometimes it rubs on the eye, whereas the absorbable ones are intracanalicular, so nothing's sticking out."

The Multidose PF Revolution

Clinicians tend to nudge patients toward preservative-free options to avoid the toxicity of BAK, which can worsen dry eye. In the past, preservative-free artificial tears were only available in single-dose vials, but thanks to developments in preservative-free multidose bottle technology, patients no longer have to deal with those tiny vials.

Unidirectional valves and air filters in multidose PF bottles ensure any remaining drops or outside contaminants don't enter or re-enter the sterile bottle. Some artificial tears with this technology include Optase Intense (Scope), Freshkote PF (Eyevance), Retain HPMC (Ocusoft), Oasis Tears PF (Oasis Medical), iVizia (Similasan), Refresh Relieva PF (Allergan), Biotrue (Bausch + Lomb), Clear Eyes Pure Relief (Prestige Consumer Healthcare) and Systane Hydration (Alcon).

"This is a really nice technology," Dr. Armstrong says. "These options tend to be a little more expensive at the outset than the single-dose vials or normal OTC artificial tears, but you can keep using the same bottle until its expiration date instead of buying a new box every month or throwing out the vials at the end of each day. The multidose bottles work very well, and patients love them. This is going to be a game-changer."

Trigeminal Nerve Stimulation

For patients who have difficulty instilling drops or are already using other topical medications, the nasal spray Tyrvaya (varenicline, Oyster Point) may provide some relief. "Tyrvaya harnesses the power of the nerves in the trigeminal nerve pathway to increase basal tear production," Dr. Massaro-Giordano explains. "The spray stimulates the nerves to create a feedback loop to the lacrimal glands to help pump out lacrimal fluid. When these tears are collected, there's extra oil and extra mucus, so it's a better tear film."

"My patients seem to like it, particularly the aqueous-deficient ones or patients who wear contact lenses," Dr. Pflugfelder says. "It provides an almost immediate increase in their tears. They can feel their eyes are moister, and its effects may last for an hour or several hours. I'd say there's a pretty high satisfaction level among these patients."

Joseph Christenbury, MD, of Eye Consultants of Atlanta, offers Tyrvaya as a third-line option or adjunct therapy to his moderate and severe dry-eye patients who grow tired of or have difficulty using drops. "I counsel patients that the nasal spray will make them sneeze," he says. "It's another promising tool to have in your basket, especially for elderly patients and those with decreased mobility."

Soothing Inflammation

When patients experience dry-eye flares, clinicians often turn to corticosteroid drops, such as Lotemax (loteprednol etabonate 0.5%, Bausch

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TABLE 3. A SAMPLE OF TREATMENTS FOR BLEPHARITIS & MEIBOMIAN GLAND DYSFUNCTION

For Blepharitis & Lid Hygiene		
BlephEx	BlephEx	A painless in-office device that helps maintain and clean the eyelid margins. Removes bacteria, biofilm and bacterial toxins. Replacement tips available.
NuLids	NuSight Medical	An at-home treatment for dry eye and lid hygiene. An oscillating tip stimulates the meibomian glands and cleans away debris.
Ocusoft Lid Scrub	Ocusoft	Contains a non-irritating formula that removes dirt, oil, debris and pollen from the eyelids.
Sterilid	TheraTears	An eyelid cleanser for removing external irritants from lids and lashes.
Avenova	NovaBay Pharmaceuticals	A hypochlorous acid wash 0.01% for long-term hygiene management of blepharitis. Kills a broad spectrum of bacteria.
Cliradex	BioTissue	A tea-tree-oil-based cleanser that relieves symptoms associated with Demodex, blepharitis, MGD, rosacea, dry eye, chalazion and other lid margin diseases. Comes in towelettes and light foam. Preservative-free.
I-Lid 'N Lash Pro	I-MED Pharma	A professional-use hydrating cleansing gel with 20% tea tree oil for removing ocular debris and intensive cleaning of the lids and lashes. Available in a 50-mL metered dose pump.
TheraPearl Eye Mask	Bausch + Lomb	A hot-and-cold therapy that helps to alleviate dry eye.
For Meibomian Gland Dysfunction		
LipiFlow	J&J Vision	A vector thermal pulsation system for treating MGD in the office. Delivers therapeutic pulsation energies to meibomian glands to liquefy and evacuate meibum.
Systane iLux2	Alcon	A handheld, portable device that targets the meibomian glands with light-based heat and compression under direct visualization in less than 12 minutes.
TearCare	SightSciences	An open-eye, blink-associated device suite that delivers consistent thermal energy to the lid structure.
MiBo Thermoflo	MiBo Medical Group	Treats dry eye by delivering consistent, emissive heat and ocular massage to the meibomian glands.
eyeXpress	Holbar Medical Products	An eye hydration system for in-office therapy. A goggle system delivers uniform, regulated heat to the lid structure.
OptiLight	Lumenis	An intense pulsed light system for MGD indicated for professional use in patients 22 or older with moderate to severe DED and with Fitzpatrick skin types I-IV.
LacryStim IPL	Quantel Medical	Intense pulsed light system that uses a unique wavelength spectrum and train of pulses to stimulate the lachrymal and meibomian glands, reduce inflammation and improve tear film quality.
Epi-C PLUS	Espansione Group	A no-gel IPL with low-level laser therapy approved for dermatological use in the U.S. For ophthalmic use, white and yellow masks stimulate lymphatics and increase drainage. Wavelength: 633 ±10 nm; emission power: 100 mW per cm2.
Thermal 1-Touch	Ocusoft	A localized heat therapy that applies heat and gentle pressure to the lids to release meibum.

+ Lomb), Eysuvis (loteprednol etabonate 0.25%, Kala) or Flarex FML (fluorometholone acetate 0.1%, Eyevance). Corticosteroids get the inflammation under control quickly so patients can begin or resume more conservative dry-eye treatments such as warm compresses or artificial tears. With a short, usually two-week, course, these are typically safe options, though clinicians emphasize the importance of checking your patient's glaucoma status before initiating any steroid treatment. Patients with a history of poor contact lens hygiene may also be poor candidates for a steroid drop.

"For patients with symptoms unresolved by artificial tears, I may put them on a maintenance medication such as Xiidra, Restasis or Cequa, depending on their insurance plan and coverage," Dr. Christenbury says. "Cequa has a higher concentration of cyclosporine than Restasis [0.09% vs. 0.05%], so sometimes that works if patients feel Restasis isn't enough, but it mainly comes down to insurance coverage. There's a generic Restasis available now, which may help reduce the cost burden."

"I use Restasis for moderate to severe aqueous-deficient dry eye because these patients have reduced goblet cell numbers," Dr. Pflugfelder says. "Any of the cyclosporine drops will increase goblet cells, which are known to be very helpful for maintaining eye health. I find Xiidra tends to be more beneficial for reducing symptoms rather than signs. Its effects on signs in the clinical trials were fairly minimal, but it can, in certain patients, provide a lot of symptomatic improvement. So, if patients have high symptom severity scores and don't respond to milder treatments (for 'level one' and/or some pulsed corticosteroids) then I would consider Xiidra."

Xiidra may be particularly helpful

for patients with both dry eye and evidence of meibomian gland disease or rosacea blepharitis, Dr. Armstrong notes. "The anti-inflammatory aspect tends to do a good job of alleviating some of these symptoms," he says. "There's no generic version of Xiidra though, so if it's pricey, I don't push it on the patient."

He adds that if patients have an underlying medical condition such as Sjögren's syndrome or lupus, where autoimmune inflammation causes severe dry eye, he's quick to offer Restasis at the first or second visit with the patient. "These patients tend to suffer from lots of dry eye," he says. "It's an immune issue where they just aren't producing tears. Sjögren's patients who start Restasis tend to do pretty well."

Expressing Meibomian Glands

MGD treatment mainstays include warm compresses, eyelid massages, manual expression and devices that heat the lids or deliver pulsed light to encourage oil egress.

Dr. Pflugfelder uses LipiFlow (J&J Vision) and Thermal 1-Touch (Ocusoft) devices in his practice. Thermal 1-Touch heats the lids and glands, which are then manually expressed. Patients return for repeat treatments about every six to eight weeks with the Thermal 1-Touch, he says. "There are reports of sustained effects for six months or longer, but it's always hard to know," he notes. "I'd say, just based on what patients prefer, it'd be about every few months, depending on out-of-pocket expenses."

"The Systane iLux2 [Alcon] is a handheld thermal device," Dr. Massaro-Giordano says. "With this device, the doctor gently squeezes the eyelid while applying heat to allow egress of the oil onto the surface of the eye." Some other thermal devices include the MiBo Thermoflo (MiBo Medical Group) and eyeXpress (Holbar Medical Products).

Intense pulsed light devices such as OptiLight (Lumenis) and LacryStim IPL (Quantel Medical) are often used in combination with thermal devices to improve MGD and the tear film. IPL devices emit pulsed light at a wavelength in the 500- to 1,200-nm range, which selectively targets chromophores in telangiectasias. This eyelid vessel destruction is thought to inhibit the access of inflammatory mediators to the meibomian glands. The heat emitted may also help oil expression and destroy inflammation-causing bacteria. Be sure to consider your patient's skin phototype before initiating IPL.

Before using a MGD device on his patients, Dr. Christenbury tries to clean up the glands and reduce inflammation with a month or so of doxycycline. "We've been using LipiFlow for years and recently got TearCare (Sight Sciences)," he says. "These devices aren't 100-percent effective, but they kickstart the patient in the right direction. They heat and express the oil in the glands more effectively than compresses alone. They're a good adjunct for your tough meibomian gland cases. Once-a-year treatments are usually enough to make a difference, but some patients prefer every six to nine months.

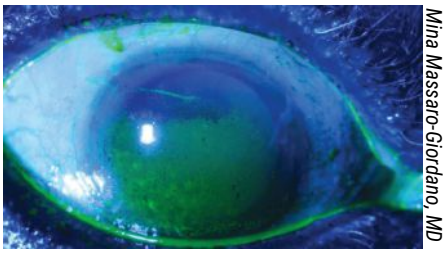
"If the MGD is severe or if there's associated ocular rosacea, I'll put patients on at least a month or two of doxycycline," Dr. Christenbury adds. "I also like using Azasite as a topical drop to reduce inflammation in the glands and on the ocular surface."

Managing Blepharitis

Pinpointing the cause of dry eye here is key. "If you just treat the eyeball when the patient has an eyelid problem—well, you can imagine how the inflamed eyelid continues to rub against the eye, exacerbating the

TABLE 4. SOME PUNCTAL PLUGS & SCLERAL LENS OPTIONS

Punctal Plugs for Aqueous Deficiency		
Vera180	Lacrivera	Synthetic, absorbable lacrimal plugs (poly-p-dioxanone) designed to provide temporary occlusion for approximately 180 days. Available in sizes of 0.2 to 0.5 mm.
Soft Plug Extended Duration	Oasis Medical	A short-term plug (less than three months). Available in sizes of 0.2 to 0.5 mm. Also available: absorbable collagen and permanent intracanalicular plugs.
Scleral Lenses for Severe Dry Eye		
PROSE	BostonSight	A gas-permeable prosthetic device that reduces dry-eye symptoms of pain and light sensitivity and supports ocular surface healing.
DigiForm	TruForm Optics & Contamac	A scleral lens made of material with a low wetting angle to alleviate dry-eye symptoms, corneal distortion and surface irregularities. Also available in Optimum Extra and Optimum Extreme.
Onefit	Blanchard Contact Lenses	A scleral lens to help alleviate end-of-day dryness symptoms and intolerance of environmental effects with soft lenses. Provides a thin fluid cushion over the eye.
Boston IV	Bausch + Lomb	A rigid, gas-permeable contact lens with a non-stick surface that resists dirt and debris. B+L says it's an economical choice for vision correction and dry eye. Other options such as the Boston XO2, XO, EO and ES have B+L's Tangible Hydra-PEG coating technology, which increases surface water retention and lubricity and minimizes deposits on the lens.



Mina Massaro-Giordano, MD

A dry cornea with punctate epithelial keratoconjunctivitis with fluorescein staining.

problem," says Dr. Massaro-Giordano. "Special ointments or steroids may help, depending on the etiology, and sometimes I give a pulsed dose of a stronger antibiotic steroid drop to treat the ocular surface. If they're having a hard time healing the surface, I may add autologous serum."

Half the battle of blepharitis is getting your patients to believe it's real, says Dr. Armstrong. "I created a PowerPoint about blepharitis to show my patients what's going on," he says. "I found that if I just talked about it and tried to describe it, patients didn't really believe it was real, but if I showed them photos of *Demodex* collarettes or redness and crusting on the eyelashes and lids, then they began to see it wasn't just this made-up thing."

Clinicians say it's critical that patients do warm compresses once or twice a day, as well as eyelid massage and lid hygiene to remove debris with therapies such as Ocusoft lid scrub and cleansers, Sterilid (TheraTears), Avenova (NovaBay Pharmaceuticals) and Cliradex (BioTissue). Cliradex, a tea-tree-oil-based cleanser may be useful for managing the symptoms associated with *Demodex* blepharitis. An at-home device called NuLids (NuSight Medical) uses an oscillating tip to clean away debris.

For in-office treatments, there are I-Lid 'N Lash Pro (I-MED Pharma), a 20% tea tree oil hydrating cleansing gel, and BlephEx (BlephEx), a device used to exfoliate along the lash line and remove inflammatory biofilm.

Autologous Therapies

Serum tears are another option for treating DED when other treatments fail. "They're a bit like superpowered artificial tears," Dr. Christenbury says. "They have nutrients and nerve growth factors, and they're regenerative." To obtain these serum tears, patients undergo a blood draw, and a compounding pharmacy spins the blood down and sends the serum tears to the patient.

"Autologous serum eye drop treatments can help heal the ocular surface, but the downside is that they're very expensive and usually not covered by insurance," Dr. Massaro-Giordano points out. "There are different amniotic membrane products and serum products, and they all kind of work similarly, where growth factors are placed on the eye, whether in drop or contact lens form, to speed up healing."

Dr. Pflugfelder frequently uses platelet-rich plasma tears in his patients. "At least in my hands, I find platelet-rich plasma to be more effective than serum tears or regular plasma," he says. He and his colleagues published a multicenter study in *The Ocular Surface* a few months ago that reported that platelet-rich plasma was highly effective at treating signs and symptoms of ocular surface diseases such as DED, neurotrophic keratopathy, dormant corneal ulcers, limbal stem cell deficiency and cicatrizing conjunctivitis.[2] Almost three-quarters of patients demonstrated an improvement in corneal staining from baseline. The number who had punctate epithelial erosions or epithelial defects dropped from 76.5 to 47 percent and from 23.5 to 7.8 percent, respectively ($p<0.0001$). SANDE score symptoms also decreased significantly at six month follow-up (median: 90 to 34.6, out of 100 points; $p<0.0001$).

Amniotic membrane is a less-often-used therapy for severe dry-eye, but proponents say it's effective. Dr. Christenbury uses cryo-preserved amniotic membrane. He says the treatment works rapidly with effects lasting for a few months. "Amniotic membrane doesn't rely on patient compliance," he points out. "It's good for healing and regenerating the ocular surface. The membrane remains on the eye for five to seven days, and then we remove it. We counsel patients that their vision will be blurry during that time."

Scleral Lenses

Scleral lenses are used frequently for moderate and severe dry eye, particularly in cases of corneal epithelial disease, Sjögren's syndrome and graft versus host disease. "There's probably nothing better for protecting the cornea, improving symptoms and decreasing light sensitivity in moderate to severe dry eye than scleral lenses," says Dr. Pflugfelder.

Scleral lenses sit on the scleral portion of the eye and vault over the cornea. "These lenses are filled with fluid, so the cornea is bathed in fluid the whole day," Dr. Massaro-Giordano says. "These work very nicely for some patients."

"We fit a variety of scleral lenses," Dr. Pflugfelder says. "The lens with the highest satisfaction rating is probably PROSE (BostonSight) because it's completely custom-fit. Unfortunately, it also tends to be the most expensive. These lenses are fit using computer-aided design to adjust the diameter or vault."

"We're lucky to be in a field where there's always new and amazing medications coming down the pipeline," says Dr. Armstrong. "We're seeing advances in topical therapies, gene therapies, and nerve stimulators. There's always something to look forward to at the next academic meeting."

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2. Soifer M, Tovar A, Wang M, et al. A multicenter report of the use of plasma rich in growth factors (PRGF) for the treatment of patients with ocular surface diseases in North America. The Ocular Surface 2022;25:40-48.

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DIAGNOSING DRY EYE: PEARLS FOR SUCCESS

There are numerous testing options available to help pinpoint the cause of signs and symptoms in patients with ocular surface disease.

LEANNE SPIEGLE
ASSOCIATE EDITOR

While diagnosing some ocular conditions can be relatively straightforward, others, such as dry eye, are multifactorial and could be caused by one of many possible etiologies. You may need to perform multiple tests on a patient with suspected dry-eye-related signs or symptoms to determine the culprit and create an effective management plan. The last thing you want to do is misdiagnose the case—or fail to thoroughly screen patients—and cause them to suffer longer than necessary.

What is your personal strategy to ensure that you properly diagnose a patient with dry eye? Which tests do you perform and when? Here, cornea specialists offer guidance to help you maximize your chances of making a proper diagnosis and identify patients in need of treatment.

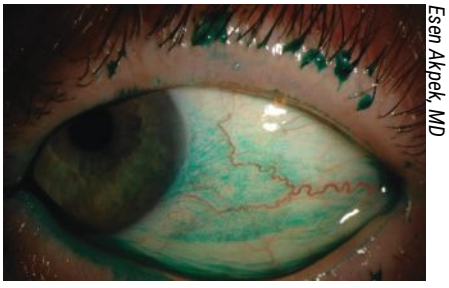
The Patient Interview

It's no secret that a solid history is one of the most important tools for any doctor to help determine where to begin and which tests to perform on a patient. Obtaining inadequate current and historical patient data or failing to ask the right questions about topics such as lifestyle, medications or symptoms can cause you to overlook information that could be critical to determining the proper testing and diagnosis of the patient's dry eye.

"Dry eye is underappreciated and underdiagnosed, and that leads to undertreatment," says Esen Akpek, MD, a professor of ophthalmology and rheumatology at Johns Hopkins University School of Medicine, and director of the Ocular Surface Disease and Dry Eye Clinic at the Wilmer Eye Institute in Baltimore. "We routinely check intraocular pressure and perform dilated exams to check the cornea, but most clinicians don't check for dry eye unless a patient complains about it."

Dr. Akpek advises, even if you don't test the ocular surface or tear film of every patient, "at the very least, we need to be asking all of our patients how their eyes feel and how their vision is when we take their history."

Here are several topics to discuss with patients that can help you determine what to focus on during the exam and steer toward a potential diagnosis:



Esen Akpek, MD

Slit-lamp appearance of an eye with 3+ lissamine green staining of the bulbar conjunctiva.

• ***Ask about symptoms.*** Christopher J. Rapuano, MD, chief of the cornea service at Wills Eye Hospital and professor of ophthalmology at the Sidney Kimmel Medical College at Thomas Jefferson University, agrees that getting a good history and understanding the patient's symptoms are key.

"I try to figure out what's going on by asking the patient questions like, 'Do your eyes feel gritty/sandy? Do they feel painful? Are they red? Do your eyes feel worse in the morning vs. afternoon or evening?'" he says. He notes that when dealing with

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Dr. Rapuano is a consultant for Avellino, Bio-Tissue, Cellularity, Dompé, Glaukos, Kala, Oyster Point, Sun Ophthalmics, Tarsus and TearLab. **Dr. Akpek** is a consultant for Novalique and an investigator for Ocular Therapeutix.

patients who have clinical dry eye, "they tend to come in presenting with the classic feeling of grittiness or sandiness that tends to worsen as the day goes on."

Another question to ask dry-eye suspects is whether they have difficulty with near work or if such tasks exacerbate their symptoms. "Dry-eye patients tend to be worse with what I call concentrated visual tasks," Dr. Rapuano explains. "These include activities such as using or playing games on the computer, tablet or cell phone, watching TV or movies, reading or driving."

Most dry-eye patients will have some version of these common symptoms (i.e., grittiness and eye strain/discomfort during near work). However, the presence or timing of specific symptoms may point you toward the possible type or severity of the condition.

"If the patient has any level of blepharitis, the eyelids tend to be red from the inflammation, and while they may have symptoms of dryness and grittiness, it tends to be worse in the mornings," says Dr. Rapuano. He adds that, prior to the exam, this is the first hint of whether you're dealing with a case of blepharitis or aqueous-deficiency. Keep in mind that lagophthalmos is another potential diagnosis for patients who experience the most ocular discomfort in the mornings.

Another important question to ask patients who complain of dry eye is what helps their symptoms improve. "Ask if artificial tears help alleviate the discomfort. If they say no, or if the drops only help for a short period of time, the patient may have blepharitis or allergies," says Dr. Rapuano.

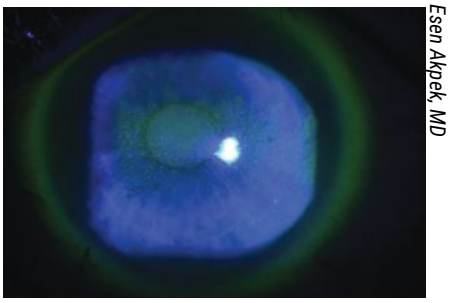
Dry eye questionnaires, such as the Ocular Surface Disease Index, SPEED questionnaire or the University of North Carolina Dry Eye Management Scale, can be efficient tools to help you gather some of this information about the patient and their symptoms before they sit down in your chair, freeing up more time for the physical exam.

Ask about allergies and medications. Allergies are potential culprits of dry-eye symptoms that'll be easier to identify through a detailed case history. "Sometimes, the ocular symptoms are related to the allergy itself, and other times, they're related to the medication the patient is taking for the allergy," Dr. Rapuano points out. To rule out this potential cause, ask the patient about any allergies they know or suspect that they have, as well as which, if any, medications they currently take or were previously on.

Besides allergy medication, there are numerous other types of drugs known to cause dry eye. "Antihistamines are probably the highest on the list when it comes to medications that cause eye dryness and related symptoms," says Dr. Rapuano. One study published earlier this year investigated various medications that seem to cause or worsen dry-eye disease, including "systemic medications such as antihistamines, antihypertensives, anxiolytics/benzodiazepines, diuretics, systemic hormones, non-steroidal anti-inflammatory drugs, systemic or inhaled corticosteroids, anticholinergic medications, isotretinoin (causes meibomian gland atrophy) and antidepressants."[1]

Dr. Akpek adds that she also occasionally sees dry eye in patients on high doses of painkillers, especially those with an underlying diagnosis of something like fibromyalgia or arthritis. "These are the patients that already have aqueous tear deficiency and a decreased blinking rate, so I try to limit their medical treatment if I can, without having an impact on other areas of their health."

Many patients fail to accurately report past and current medication or drug use in their paperwork, one reason being they may think it's irrelevant or are afraid they might be told to discontinue using their medication. "If you do suspect that a patient's medication may be causing or contributing to their symptoms, reassure them that this doesn't mean they need to stop the medication, but we may have to compensate by using a prescription drop like Restasis or Xiidra," notes Dr. Rapuano.



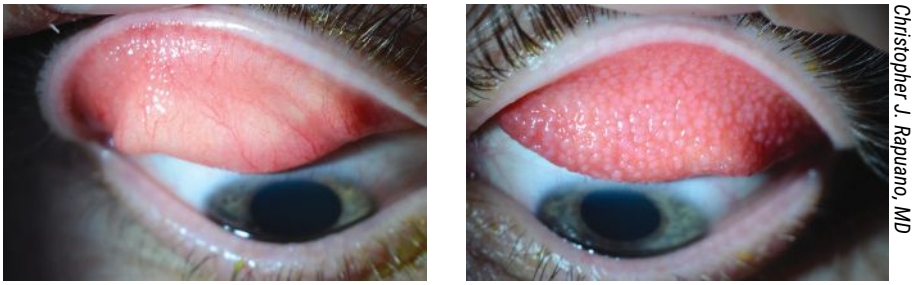
Esen Akpek, MD

Slit-lamp appearance of a cornea with 3+ central macro epithelial erosions, under cobalt blue light.

Ask about contact lens wear. "Contact lens wear can certainly cause dry eye; it's associated with increased risk of blepharitis," Dr. Rapuano points out. "Some people say their eyes feel better when they put contact lenses in, and others say it makes them feel worse." For patients who do seem to have ocular discomfort relating to their contact lenses, he notes that switching them from reusable to daily disposable lenses will help avoid protein buildup and eliminate the need for disinfecting solution that could be irritating the eye. Decreasing the time of wear—for example, from 16 hours a day to eight hours—could also be a viable suggestion for patients whose symptoms seem to worsen throughout a day of lens wear.

Similar to how patients may be hesitant to answer truthfully when asked about medications, the same goes for questions regarding their contact lenses; some may fear they'll be instructed to stop wearing them. Dr. Rapuano notes that most of the time, switching the lens type or material or changing wear habits can help alleviate the issue. However, he does recommend discontinuing wear in more severe cases of dry eye if you suspect contact lenses are the cause.

Ask about surgical history. "Often when you ask patients if they've had ocular surgery, they'll say no," says Dr. Rapuano. "Then, you ask them if they've had LASIK, and they'll say 'oh yeah, I got that a few years



Christopher J. Rapuano, MD

This patient's left upper lid (right photo) shows moderate to severe allergic conjunctivitis related to contact lens wear seen by the clearly visible allergy bumps. Under the right eyelid of the same patient (left photo), a mild case of allergic conjunctivitis can be observed.

ago; I forgot to mention it.' The other surgery to specifically ask your patients about is eyelid surgery. They often won't remember that they had their lids lifted, or they just don't want to admit it." Even if the patient's paperwork reflects that they have no surgical history, be sure to ask again in the exam room.

The Examination

Once you have a thorough case history and symptom report, the next step toward a diagnosis is the physical examination.

According to Dr. Akpek, examining patients for signs of dry eye shouldn't only be for individuals who report experiencing symptoms. "Some patients may never report symptoms to their doctor because they assume that it's normal or due to allergies or aging, which is a major reason why underdiagnosis is so common," she says. For this reason, she suggests that "observing the ocular surface and tear film should be part of a comprehensive eye examination."

For Dr. Akpek, after taking the patient's history, she performs the following minimum battery of tests: tear osmolarity (done by the technician), unanesthetized Schirmer's test, tear-film breakup time and pattern with fluorescein, corneal fluorescein staining (checking the score after two or two and a half minutes) and conjunctival lissamine green staining—both according to the ocular staining score—and, lastly, meibomian gland examination and meibum score.

Dr. Rapuano says that when he first performs an exam on a patient to evaluate signs of dry eye, "I first look at the eyelids for signs of anterior blepharitis, posterior blepharitis or *Demodex*. I find it critically important to flip the lids. Have the patient look up and look under the lower lid. You might see allergy bumps even in patients who you didn't suspect had an allergy," he points out.

What's even more important is flipping the upper lid, Dr. Rapauno suggests. "For a lot of patients who have nonspecific dry-eye symptoms, when you flip the upper lid, you might find something you weren't expecting," he says. "For example, you may find that they have floppy eyelid syndrome, where the eyelids are super lax, but they just kind of divert overnight, and the patient will often have worse symptoms in the morning." He adds that looking under the upper lid could also reveal allergy bumps, signs of giant papillary conjunctivitis from contact lens wear or less common conditions such as vernal keratoconjunctivitis. Flipping both of the lids can also reveal signs of superior limbic keratoconjunctivitis, says Dr. Akpek.

Rarer diseases can also be detected via observing the eyelids. "When you have the patient look down and lift the lids, you can look at the superior conjunctiva, and you may find superior limbic keratoconjunctivitis," says Dr. Rapuano. "Or, when you have the patient look up and examine the inferior lid, you may be surprised to find that there's scarring and possibly foreshortening of the inferior conjunctival fornix, which can be indicative of an early pemphigoid situation."

Pemphigoid is a rare autoimmune condition that can affect patients at any age but tends to be most prevalent in those older than 60.[2] Signs of ocular cicatricial pemphigoid, affecting 60 to 70 percent of people with mucous membrane pemphigoid, include bilateral conjunctival cicatrization or scarring. "It's a very serious, progressive disease that starts with mild signs and symptoms," says Dr. Rapuano. "If you catch it early, it's much easier to treat before it causes a large amount of scarring and potentially results in loss of vision."

Decoding the Staining Pattern

Evaluating the tear film using trusty fluorescein dye can help you determine if the dry-eye symptoms are due to an aqueous deficiency or another cause. "If I look at the tear film and it's basically non-existent or there's no good tear lake, then it's more likely a case of aqueous-deficient dry eye," notes Dr. Rapuano. "If there's significant punctate staining on the cornea, that indicates ocular surface disease. The staining pattern may help you determine whether it's more superficial punctate keratitis, which is often superior. If it's a poor blink, it'll be kind of central or inferior SPK. If the staining is more diffuse, it could be dry-eye disease or SPK."

Next, Dr. Rapuano uses lissamine green to highlight any conjunctival problems. "There are some patients where you'll put fluorescein in the cornea, and everything looks pretty normal," he says. "But then, you put the lissamine green stain in, and the conjunctiva lights up with significant damage. That tells you that there's some serious ocular surface disease going on, which you may not have noticed by staining only with fluorescein." Dr. Akpek adds that "conjunctival staining is an indicator of inflammatory dry eye and is commonly seen in Sjögren's and other autoimmune conditions, such as rheumatoid sclero-

derma or graft versus host disease."

Dr. Akpek, who also recommends staining with both fluorescein and lissamine green, uses a yellow filter to more clearly observe the corneal staining pattern. She notes that while corneal staining may not ascertain the cause of the dry eye, "the impact of staining is high when it comes to symptoms of discomfort, pain or vision-related quality of life." She continues, "If the central staining score is high, I suspect a patient has vision difficulty, while staining anywhere on the cornea can indicate pain. Central staining could be suggestive of an aqueous deficiency, but if a patient has decreased blinking rates, such as from Alzheimer's or Parkinson's, they may also have central staining."

In summary, Dr. Akpek notes that "the staining pattern depends on what you find in the rest of the exam. You need to perform a good, comprehensive exam to understand what the pattern means."

Meibomian Gland Dysfunction

As a leading cause of dry-eye disease, this differential is one that must always be considered when patients complain of ocular dryness or discomfort. Physically examining the eyelids and meibomian glands may suggest whether the dry eye may be a result of MGD. However, the best way to confirm or deny the presence of this condition is by squeezing the lids to see what kind of secretions are produced by the meibomian glands.

"If I can't get any secretions, that's bad, and that tells me that there's significant MGD," says Dr. Rapuano. "If I get thickened, sort of unhealthy secretions, I know that the glands are functioning, but they're not functioning very well. If I get great secretions, then I assume it's less likely that the dry eye is an MGD-related issue."

Neurotrophic Keratitis

"One condition that we've been focusing more on in the past several years is neurotrophic keratitis," Dr. Rapuano says. "You have to ask yourself, 'is the patient neurotrophic? Is there a component of neurotrophic keratitis that's possibly giving them the ocular surface disease?'" He notes that if staining reveals a fairly diffuse SPK but the patient isn't as symptomatic as you would expect, consider this differential. Various ocular and systemic conditions are commonly seen in patients who develop neurotrophic keratitis including diabetes, herpes simplex, herpes zoster, chronic dry eye, multiple surgeries and neurological problems such as stroke.

The easiest way to test corneal sensation is by touching the patient's eye with the cotton end of a Q-tip and asking if or how much they can feel it. If you plan to test the patient's corneal sensation, be sure to communicate to the technician that it'll need to be completed before the patient receives numbing drops.

Objective Dry-Eye Tests

Physicians also add one or more objective tests to help pin down a diagnosis and/or the severity of the patient's condition.

• ***Osmolarity testing.*** This test is sometimes used to help determine which patients may have clinical dry eye. A recent study evaluated the performance of two osmometers on the market—Trukera Medical (formerly TearLab) and I-Pen—and found that both instruments have good accuracy and repeatability *in vitro*, though repeatability did decline past mid-range osmolarities.[3]

Just last month, Trukera Medical announced its new ScoutPro osmolarity system, which is the first portable osmometer in the United States. Using any of these devices may be helpful to confirm whether a certain dry-eye treatment is working by allowing you to objectively measure a change in tear osmolarity.

In a poster presentation from the 2009 American Academy of Ophthalmology meeting, Foulks et al found that the cut-off value for moderate to severe dry-eye disease for the Trukera osmolarity system is 316 mOsm/L, while a value between 308 mOsm/L and 316 mOsm/L indicates mild dry eye. According to research on the I-Pen osmolarity system, a cutoff value of 318 mOsm/L was recommended to diagnose clinical dry eye.[4]

• ***LipiView.*** This interferometer from J&J Vision/TearScience captures both photos and videos of the meibomian glands that allow you to measure the thickness of the lipid layer in tears, assess blink dynamics and observe meibomian gland structure, all of which can be useful metrics to help evaluate and diagnose dry-eye disease. Clinical research characterizes a lipid layer of less than 60 nm as thin, between 60 nm and 100 nm as normal and 100 nm or above as thick. One study reported that three of four patients who report severe dry-eye symptoms have thin lipid layers of 60 nm or less, while roughly three of four patients without symptoms have relatively thick lipid layers of 75 nm or greater.[5] However, other research has also shown that those on the other end of the spectrum with thick lipid layers may be suffering from dry-eye disease, too. Data from one study revealed that ocular surface staining and tear-film breakup time were significantly worse in those with thick lipid layers than in those with thicknesses in the normal range.[6]

• ***Matrix metalloproteinase 9 (MMP-9) tear testing.*** This diagnostic tool helps identify patients with ocular surface inflammation. One study found that the results of the MMP-9 test correlated well with subjective symptoms evaluated by the OSDI (p=0.001), tear-film breakup time less than five seconds (p<0.013), Schirmer's test (p<0.001), conjunctival staining (p<0.001) and corneal staining (p=0.007).[7]

"If I've been treating a patient with a small amount of inflammation and I'm considering starting them on steroids, I might use the MMP-9 test to confirm whether there really is inflammation going on," says Dr. Rapuano. As with the tear osmolarity

(Continued on p. 78)

OFFICE-BASED SURGERY: TALES FROM THE FRONT

Surgeons share their experiences setting up and utilizing an in-office surgical suite.

CHRISTOPHER KENT
SENIOR EDITOR

It's no secret that some cataract—and now retina—practices have opted to create in-office surgical suites. Proponents say offering in-office surgery gives them increased flexibility as well as staff and equipment advantages compared to hospitals or ASCs. Other physicians wonder, however, about the specter of endophthalmitis, anesthesia problems, reimbursement issues and other concerns.

Here, to help shed light on this evolving situation, several surgeons, one of them a retina specialist, share their stories about going down this path, and discuss the questions that often come up when surgeons consider doing this.

Bringing Surgery In-house

Orest Krajnyk, MD, a board-certified cataract and refractive surgeon in New Smyrna Beach, Florida, and a physician CEO graduate from Kellogg Business School, set up his in-office surgery center three years ago. He explains that his family had decided to move to the east coast of Florida. "At an ophthalmology meeting I heard a discussion about setting up an ASC in New Smyrna Beach because the doctors were tired of having to do surgery in local hospitals," he says.

"I ended up meeting Tony Burns, MBA, CASA, CSFA, who had built several ASCs and begun setting up in-office surgery suites," he continues. "He said that getting 10 doctors to set up a surgery center would be much more of a challenge than we realized, and it turned out he was right. Tony and I stayed in touch, and one day he offered to make me the first client of a new in-office surgical set-up company he'd started, iOR Partners.

"There was extra space available next door to our office, so I took that over and set up there," he says. "In June of 2019 I opened up my in-office surgery center, with two ORs, a clean-and-dirty room in the middle, and a preop-postop area in front of it with massage chairs. The whole project cost 10 or 20 percent of what it would have cost to build an ASC.

"I was a little nervous," he notes. "Being the first practice to work with iOR was a leap of faith, but I trusted the people I was working with. They came in, credentialed us and helped us set everything up. If there are complications, we have a protocol. And we're certified by the American Association for Accreditation of Ambulatory Surgery Facilities, so it's not like we're just doing this casually."

Dr. Krajnyk says he currently uses the surgical suite once a week. "If it gets busier, I can add days as needed," he notes. "I do 15 to 20 cataracts a week or so, all in one day. I start at about 8:30 and I'm usually done by 2 or 3 o'clock."

Dr. Krajnyk recalls that when it was time to reopen after the six-week COVID shutdown, he was the first cataract surgeon in his area to be back up and running. "I was operating one day after the shutdown ended, and I was caught up within the first week," he says. "Some of my colleagues had to wait two months after reopening to do surgery because the surgery center said, 'Cataract surgery is elective surgery. You can't do it yet.'

This article has no commercial sponsorship.

Dr. Melendez consults for Alcon, Zeiss, Allergan, Ocular Sciences and RxSight. He reports no financial ties to iOR Partners. **Dr. Krajnyk** owns shares of iOR Partners. **Dr. Durrie** is chairman at iOR Partners. **Dr. Feistmann** reports no relevant financial ties.

"I've now done more than 1,300 cataract surgeries in our surgical suite," he concludes. "I've had zero infections, zero vitrectomies and no complications. My staff knows exactly what to do. And we've done well financially because we're in control of our own equipment, costs and reimbursement. Furthermore, I have the only in-office surgery center in this county. Patients are often very impressed that we've done this in our tiny little community, so it's a marketing tool as well. I wouldn't think twice about making that decision again."

Dr. Krajnyk says although it's possible to set up an in-office surgical center on your own, he believes it might not be advisable. "I've seen people do it and it turned out OK," he says. "But it's a tradeoff; you spend less money but a lot more time solving problems and finding the right way to do something. And, with outside help, the agency shares some of the liability if something goes wrong."

Orest Krajnyk, MD

Orest Krajnyk, MD, says his in-office surgical suite is profitable, thanks in part to his being in control of equipment and costs. He also uses it as a marketing tool. His OR features adjustable-color lighting to help patients relax.

Striking Out on His Own

Robert F. Melendez, MD, MBA, the CEO and founder of the Juliette Eye Institute in Albuquerque, New Mexico, which has its own surgical center, says he was part of a very large practice for 16 years, where he did 2,000 cataracts per year. "The average surgeon does 300 to 500 per year," he notes. "I did 32 per day. I thought that was normal.

"When I decided to start my own practice two years ago, COVID hit," he continues. "I believe that patients prefer a more 'premium' experience, so I looked at ways to make that possible. I wanted to have a great website, a new building, the newest technologies and customer service that would knock patients' socks off, and offering office-based cataract surgery seemed like a great way to enhance the patient experience. Sending them out to a surgery center is the way it's always been done, but that doesn't mean we should continue down that road." Coincidentally—Dr. Melendez also wound up working with iOR Partners.

"They helped us check all the boxes and stay organized, get the proper accreditation and figure out what committees we needed to have in place," he says. "They also provided a very robust EHR system that tracks all of the information from inventory to the patient's operative status and the results of the history and physical we do. Then they helped us with coding and billing. This has made it very seamless for us, which allows us to spend more time with the patient, enhancing their experience. The company will also train your office's staff, if need be.

"When I started my new practice, I predicted that I'd do about 40 percent of my cases in my office-based surgery suite and 60 percent in the local ASC," he notes. "But as I started doing in-office surgery, I realized that I could do most of my patients here. The only exceptions were patients with uncontrolled comorbidities and serious illnesses. Those patients should be done in a surgery center with an IV, giving them more sedation and a more controlled environment.

"I was shocked by how effective office-based surgery is, how safe it is, and the great outcomes we've produced," he says. "If you'd told me a couple of years ago that I'd be doing office-based surgery, I would have said you were crazy. I wasn't aware of anyone doing that here in New Mexico. Now, three of my friends have started office-based surgery suites in the past year."

Dr. Melendez says patients are thrilled to be able to get their surgery done at his office. "The patient experience is definitely enhanced with office-based surgery," he says. "Patients come to the same location as they do when I see them in the clinic, so their anxiety level is already diminished. They don't have to drive to a different surgery center, get lost and end up running late, which gets them all worked up by the time they get there on the day of surgery.

"In fact, we've found that patients require less sedation, which creates an overall better patient experience," he continues. "Patients get to see the same staff they just saw two or three weeks prior for the exam, and patients know them."

Managing Retinal Emergencies

Another group of doctors who might benefit from having an in-office

Robert F. Melendez, MD, MBA

Robert Melendez, MD, MBA, says his in-office suite is perfect for his premium practice. He says the majority of his cataract surgeries can be done there, and patients are very happy—even requiring less sedation during surgery.

surgical suite is retina specialists. Jonathan Feistmann, MD, a retinal specialist practicing at NYC Retina in New York City, and his partner, Julia Shulman, MD, set up their own in-office surgical suite earlier this year. His story clearly illustrates the potential benefits of this situation.

"The reason we're doing office-based surgery is out of need," he explains. "As retina specialists, patients are frequently sent to us with urgent, time-sensitive retina emergencies such as retinal detachments. We get calls like this several times a week. We're faced with an individual freaking out because they're losing their vision, and of course they want it fixed right away.

"Before we had our in-office surgical suite, my concern in this situation wasn't so much about the retinal detachment, because I know I can fix that," he continues. "My concern was getting time in an OR—figuring out where to take the patient and when we could get the patient in. When this happens in the middle of a busy day, we suddenly have multiple staff stopping what they were doing to make frantic phone calls to surgery centers and hospitals and essentially beg for time in their OR. Most often the response is, 'There's no availability,' or 'We're closing for the day. Can you do it tomorrow?' In addition, there's time-consuming paperwork and other requirements.

"In the past," Dr. Feistmann says, "I've often told my patients, 'I'm ready to go and you're ready to go; we just need an operating room that will let us in.' We work with very good people at our local hospitals and surgery centers. They've been very accommodating, and they always try to help us as best they can. But in a lot of ways they're limited, because surgery centers close in the early afternoon. Hospitals are also trying to close their ORs for the day and be efficient with staff and resources and finances. Dealing with emergencies is seldom profitable.

"For example, before we opened our OR, near the end of construction, we had a 41-year-old radiologist visiting from Texas who had a superior bullous fovea-on retinal detachment," Dr. Feistmann recalls. "He came in at 7:00 a.m. on a Friday morning, and our clinic was very busy. A radiologist depends entirely on his or her eyes, so potentially losing your vision is very scary; if you're visually impaired, you're out of a job. So he was understandably very upset.

"I told him to get on the next flight back to Texas, and that his doctor would be waiting to take him straight to the OR," Dr. Feistmann continues. "I told him that with a gas bubble in his eye following the surgery, he wouldn't be able to fly home. However, his vision was getting worse by the hour and he didn't want to wait until the evening. He said that he'd be willing drive from New York to Texas just to get the surgery done right now.

"Unfortunately, our OR wasn't finished yet, so I had to call the hospital myself and beg them to squeeze him in," he recalls. "I knew there was OR time available because my partner happened to be in the OR and had just had a cancelation. However, the anesthesiologist told me there was no OR time available, and the patient would have to wait until the evening. When I asked why my patient couldn't just take the slot that was opened by the cancelation, he responded that it was 'hospital policy.' Clearly the 'hospital policy' was meant to disincentivize us from calling them with urgent cases. I had to tell my patient's story to strike an emotional nerve and convince them to find a slot.

"Fortunately, after an hour of begging and making my other patients wait, my partner was able to operate around noon," Dr. Feistmann says. "The radiologist was thrilled. He said losing his vision would have impacted his entire family. But if our office-based surgical suite had been available, the surgery would already have been done."

"We certainly don't handle emergencies for the money; we do it because it's part of our responsibility as doctors," Dr. Feistmann points out. "It's part of our job. But for businesses, handling emergencies is problematic. It's not like patients going to an ER, where every visit produces a lot of money. The reimbursement to facilities isn't

GA: Recognizing the Burden

Peer Perspective with Dr Nancy Holekamp, Director of Retina Services at the Pepose Vision Institute

Sponsored by Apellis Pharmaceuticals

A 2021 survey of those living with geographic atrophy (GA) revealed that this disease has a profound effect on patients' lives, resulting in a large emotional burden and loss of independence. The global Geographic Atrophy Insights Survey (GAINS) (N=203), conducted by The Harris Poll and sponsored by Apellis Pharmaceuticals, found that for nearly 7 in 10 (68%) people living with GA, the impact of vision decline on their independence and quality of life is worse than they expected. There are several reasons for this, which we will explore in the following pages. To alleviate the added burden of misunderstanding or miscommunication, thinking about phrasing key clinical terms in a way that makes them easier for patients to grasp is an important consideration.[1,2]

Dispel GA Misconceptions

GA is not a well-understood disease. In fact, the GAINS survey found that respondents lacked basic information about GA, which could lead to significant consequences. For example, 76% of patients reported that they attributed their vision loss, prior to their diagnosis, to a natural part of aging. Half of patients (50%) were also under the assumption that wet AMD is the only form of AMD that can lead to vision loss. To that end, patients need a more accurate and comprehensive understanding of GA. Indeed, at diagnosis, patients express a strong desire for more information to better understand GA. In the current study, 86% of patients wish there were more educational materials for both patients and caregivers. Furthermore, patients want to know how progression can impact their lives. Specifically, 83% said they wish they knew at the time of diagnosis the irreversible impact GA would have on their vision.[1]

76% of people living with GA agree that prior to their diagnosis, **they attributed their vision loss to a natural part of aging***

86% **wish there were more educational materials** available for patients and caregivers

83% At the time of diagnosis, wish they understood **the irreversible impact GA would have on their vision**

**All statistical graphics in this article are from the GAINS study (N=203)*

Although we need to communicate the facts about GA, we should also be conscious of how we talk to our patients. One way we simplify communication and reduce misunderstandings at our clinic is to clearly explain what geographic atrophy is at the initial diagnosis. After that, I keep things simple with patients and use the term "GA," rather than "geographic atrophy" or "dry AMD." It may seem like a small thing, but whatever we can do to make the vocabulary easier for patients is worth considering. That said, even simple terms like "blindness" can be misunderstood. When patients hear this word, they think complete darkness, which can make coping with GA much more difficult. Granted, it is challenging to explain the nature of GA vision loss. It's not like wet AMD, where you can show patients a picture simulating the central distortion and blurred area caused by leakage from abnormal blood vessels. GA can produce scotomas, which are experienced as missing vision or lack of resolution. That's very difficult for patients to conceptualize and verbalize, which only adds to our difficulties in communicating about GA and how it affects vision. Also, no two people experience a GA scotoma the same way. Every scotoma is different.[2,3]

As ECPs, we have some misconceptions too. Best corrected visual acuity is widely accepted by the clinical community and regulatory authorities worldwide as a key measure of visual function. However, this is a measure of central acuity of the fovea, and is poorly correlated with GA lesion size. Best-corrected visual acuity does not assess all nuances of comprehensive visual function. GA can grow in a unique, foveal sparing pattern that tends to involve the fovea only late in the course of the disease. Snellen visual acuity measurements do not capture GA. Just because a patient can pick out letters on an eye chart doesn't mean they can read a book or feel comfortable driving. Other measurements are needed. This is also evidenced in The Harris Poll findings. Specifically, nearly 1 in 3 (31%) patients said their vision started to decline or worsen prior to diagnosis with GA. Similarly, it's important to consider all the ways that GA is experienced by patients—beyond visual acuity loss. The survey results elucidate this as well. Specifically, patients most commonly note that they need brighter light when reading or doing close-up work (85%) and that they also experience an inability to drive at night (ie, in the dark) (83%).[1,4]

83% of patients note that they experience **the inability to drive at night**

Progression of Vision Loss Is Urgent

In contrast to the medical community's perception of GA being a disease that progresses slowly, most patients in GAINS perceive the disease as advancing more quickly than they had originally expected. In fact, most patients surveyed by The Harris Poll were surprised by the severity and speed of the disease's impact on their vision. Specifically, 77% said that the impact on their vision happened faster than they expected and 68% said the impact of the vision decline on their quality of life and independence is worse than they expected.[1]

agree the **impact** of vision decline on **QOL** and **independence** is **worse than they expected**

As clinicians, we talk about GA being a slow-moving disease because we are comparing it to the faster progression of vision loss with untreated wet AMD, but patients may not be able to relate to this. We need to rethink how we describe disease progression. From the patient's perspective, vision loss may occur surprisingly fast because it's closely tied to their experience of the world and their quality of life. With that in mind, when discussing GA with patients, it's much clearer to explain what it will be like to experience the loss. Consider that the GAINS survey found 70% of patients rely on a caregiver to help with various tasks—most commonly driving at night (42%) or during the day (33%).[1] Any loss of independence is likely to substantially impact their quality of life.

70% of patients **rely on a caregiver to help with various tasks**

"In contrast to the medical community's perception of GA being a disease that progresses slowly, most patients in GAINS perceive the disease as advancing more quickly than they had originally expected."

~8 out of **10** (77%) agree their vision was impacted **faster than they expected**

"It may seem like a small thing, but whatever we can do to make the vocabulary easier for patients is worth considering."

Acknowledge Loss of Independence

Many of our GA patients' needs are met by spouses, sons, daughters and other caregivers. This might include driving them to medical appointments, shopping and preparing meals, reading mail, paying bills, and more. Adult children wonder when they should "take away" the car keys, write all of the checks, put out medications, and manage all the little things that we often take for granted but are indicators of our independence. Caregivers may perceive all of this responsibility as a burden, but in my experience, it's also often uncomfortable for the GA patients who don't want to rely on others, particularly their children.[1]

In patients who have GA, loss of independence may not be something that families grapple with decades after a diagnosis. It can happen much more quickly. On average, surveyed patients started relying on caregiver support as early as 2.6 years following diagnosis. In the US, caregiver dependency begins just 1.6 years on average after diagnosis. But asking for this help isn't easy. Although two-thirds (68%) of patients feel dependent on others due to their vision loss, more than half (53%) feel uncomfortable asking for help.[1]

1.6 YEARS In the US, **caregiver dependency begins just 1.6 years after diagnosis on average**

Of course, not everybody has a strong support network. Some patients have no one to turn to for the level of care they need with GA. We see this all the time in our clinic. As the patient's vision gets worse, they take a bus or a taxi to their appointment. In my clinic, we sometimes see patients who are struggling with personal grooming—through no fault of their own. It's important to look out for these subtle cues. When you talk to these patients, they might share that they're also having difficulty keeping their houses clean. In many cases, these patients may have to move into assisted living, which can be very difficult for those who cherish their independence or have lived in their family home for a long time.[1]

Recognize Emotional Toll

Most patients surveyed by The Harris Poll (68%) find it hard to enjoy life as much as they had prior to their GA diagnosis. For example, many report that the disease has a major or moderate negative impact on their ability to pursue activities such as driving (74%), reading (68%), traveling (62%), hobbies and social activities (43%), and the ability to work or volunteer (42%). Consequently, patients most commonly report feeling anxious (46%), powerless (39%), or frustrated (33%) as a result of their vision loss or impairment. Indeed, GA can have a deep emotional toll, so much so that about 1 in 3 (35%) patients reported that they had withdrawn from their social lives due to their condition.[1]

~1 in **3** (35%) **withdrew** from their **social lives** due to their condition

The atmosphere in the exam room often reflects this. When you're with a GA patient, the office visits tend to be very muted and the tone of the office visit is one of empathy and sympathy. Sometimes, patients are depressed and therefore quiet, and you have to rely on what the caregiver is noticing. It's a drain on everyone—medical staff included. As doctors, we know it's our job to help, yet our options are currently very limited. Meanwhile, it's a race against the clock as patients continue to progressively and irreversibly lose vision.[1,5]

68% of patients **find it hard to enjoy life as much as they had prior to their GA diagnosis**

"As clinicians, we talk about GA being a slow-moving disease because we are comparing it to the faster progression of vision loss with untreated wet AMD, but patients may not be able to relate to this."

Keeping a Positive Attitude

Mustering optimism can be a challenge in these circumstances, but I try to be forward thinking because I know that we must do everything we can to help these patients. This begins with awareness. We need to educate our patients about the realities of GA. GAINS found that 91% want more information and options about GA to feel empowered to take control of their disease.[1]

91% want more information and options about GA to feel empowered to take control of their disease

We can also do more to bring attention to GA within our profession. My hope is that one day we will be with GA where we are with wet AMD. In the meantime, it's important to recognize that there are really big differences in patient experiences with these 2 conditions and in how we need to approach care and communication. As with any disease, the earlier we detect it, the better. This will require further education of all primary eye care providers and increased utilization of non-invasive imaging techniques such as fundus autofluorescence and spectral domain OCT. We need to advocate for our patients by educating our peers about the importance of early detection and early action.[6,7]

Dr Holekamp is director of retina services at Pepose Vision Institute, Saint Louis, MO

This article was developed in conjunction with and sponsored by Apellis Pharmaceuticals, based on an interview with Dr Nancy Holekamp. Dr Holekamp received a fee for her participation

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Survey Design

The global Geographic Atrophy Insights Survey (GAINS) was sponsored by Apellis and conducted by The Harris Poll between October 12 to December 10, 2021. To accommodate visually impaired respondents, the survey was conducted online and via the telephone among 203 participants aged 60 or over (mean age 70 years) residing in the US, UK, France, Germany, Italy, the Netherlands, Sweden, Canada, and Australia who self-reported that they have been diagnosed with age-related macular degeneration (AMD) and have dry AMD in at least 1 of their eyes. They must also have indicated that they have advanced atrophic age-related macular degeneration or advanced atrophic AMD, advanced/late/late-stage dry age-related macular degeneration or advanced dry AMD, or geographic atrophy (GA) in 1 or both of their eyes. Included patients must have been currently experiencing at least 3 GA symptoms and currently do/used to do/or have been suggested by an eye care professional but have not done at least one of the following: Take a high-dose formulation of antioxidant vitamins and minerals, stop smoking, maintain a healthy weight and exercise regularly, choose a healthy diet, manage other medical conditions, have check-ups of the retina regularly, or wear sunglasses with UV protection. Included patients must not have been diagnosed with glaucoma, Stargardt disease, or dementia, or be receiving regular injections into the affected eye every 4 to 6 weeks.

Raw data were not weighted at the individual country level and are therefore only representative of the individuals who completed the survey. For the global total, a post-weight was applied to adjust for the relative size of each country's adult population within the total adult population across all countries surveyed.

Respondents for this survey were selected from among those who have agreed to participate in our surveys. The sampling precision of Harris online polls is measured by using a Bayesian credible interval. For this study, the sample data is accurate to within ±7.8 percentage points using a 95% confidence level and ±6.5 percentage points using a 90% confidence level. This credible interval will be wider among subsets of the surveyed population of interest.

All sample surveys and polls, whether or not they use probability sampling, are subject to other multiple sources of error which are most often not possible to quantify or estimate, including, but not limited to coverage error, error associated with nonresponse, error associated with question wording and response options, and post-survey weighting and adjustments.

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sufficient for them to keep staff on for extra hours to manage a retinal emergency. So, our access to these facilities seems to keep shrinking. At the same time, we have more patients and more emergencies to deal with. I found myself wondering how we were going to deal with this for the rest of my career."

Moving Retinal Surgery In-house

Dr. Feistmann says the obvious answer was to have an in-office surgical suite that he has access to 24/7, 365 days a year. "We took it upon ourselves to research this possibility," he says. "Surgeons have been doing office-based surgery for about 10 years, so there's a lot of data out there, including the Kaiser Permanente data[1] and data gathered by iOR Partners. Tom Aaberg, MD, in Michigan published a report about doing 30 cases using office-based surgery back in 2014. I've also spoken to lots of other surgeons who've done it, including Omar R. Shakir, MD, MBA, a retina specialist in Greenwich, Connecticut, who also does cataract surgery. He told me about his experience and made it clear that it can be done and that it's safe. That gave me the confidence to proceed."

Dr. Feistmann says their in-office surgical suite opened for business on May 24th of this year. "To date, we've repaired 18 fovea-on retinal detachments," he says. "We've been able to start the surgery within two to nine hours after the patient checks into our office, usually closer to four or five hours. On at least a couple of occasions we've gotten the patient onto the operating table in less than two hours after being notified that he or she was coming in with an emergency. There's data that shows the sooner you address a detachment, the better the outcome, so we're proud of that.

"The beauty of this is that when we get the phone call, there's zero stress for me or the staff or the patient about when and where we're going to do the surgery," he continues. "We tell the patient that we'll do it right here and we'll get it done today. Instead of spending time on the phone calling people and begging for a slot, our staff can spend their time and energy taking care of the patient and getting things ready for the surgery. This has been very gratifying for me and the staff. The patients are very happy, and we've had excellent outcomes. We've done 92 cases to date, and we've had no infections, complications or adverse events."

Jonathan Feistmann, MD

Retina specialist Jonathan Feistmann, MD, says his in-office surgical suite allows him to manage retinal emergencies without having to beg local hospitals and ASCs to find an open time slot for him to help the emergency patient.

But what do his patients think? "Patients are very happy to be able to take care of their problem in the office," he says. "I was expecting some push-back, but apparently our patients have always expected it to be done in the office. So now when I say where the surgery is happening, they say, 'Great!' "

Is Office-based Surgery Safe?

Dr. Melendez says that some people seem to think that in-office surgery is done in an exam room. "Nothing could be further from the truth," he says. "Our OR is a completely sterile environment. It's all approved by the same accrediting bodies that approve ASCs.

"We have a sterile operating room next to our LASIK suite," he explains. "Next to that is a clean-and-dirty room, just like in a surgery center. We use the same equipment, with the same special paint on the walls and floors. It's a standard operating room that just happens to be at the end of my building. In addition, some of my staff have worked in surgery centers for 25 years, so we know sterile procedure.

"To date we've done almost 1,000 surgeries in our office-based surgery suite," he adds. "We've had zero cases of endophthalmitis."

"When we say we have an office-based operating room, we're not talking about doing surgery in an exam chair or in an exam room," notes Dr. Feistmann. "It's an OR just like the OR in an ASC or hospital, with the same equipment and same sterile procedures. The key difference for us is that it's connected to our office and we have access to it 24/7. Of course, there are services an ASC or hospital can offer that we can't, but those resources generally aren't relevant for ophthalmic surgery.

"Safety is something we're con-

WHAT'S REQUIRED TO PROCEED?

For surgeons considering taking the plunge into owning their own in-office surgical suite, a big question is what kind of investment in time, money and space is required to make this happen. Daniel S. Durrie, MD, founder of Durrie Vision in Kansas City and chairman at iOR Partners, explains.

"Building an ambulatory surgery center for ophthalmology surgery usually costs anywhere from $2.5 to $4 million," Dr. Durrie says. "You can build an office-based suite with the same OR specifications and equipment for $250,000 to $400,000. In terms of making back your investment, the break-even point for an ASC is 100 to 120 cases per month. In contrast, the break-even for an office-based surgery center is 30 to 35 cases per month.

"In terms of the space you'd need in order to set up a basic in-office surgical center, that differs depending on the configuration of the space and your equipment choices," he continues. "The minimum space is usually between 600 and 1,250 square feet, depending on whether you want one or two ORs. We usually require a minimum of 12 weeks to launch an in-office surgical suite, assuming there are no unusual complicating factors at the location or pandemic-related construction slowdowns. Typically, our launches happen between 12 weeks and six months after signing an agreement.

Robert F. Melendez, MD, MBA, the CEO and founder of the Juliette Eye Institute in Albuquerque, New Mexico, explains that for an in-office surgery center you need an operating room, a clean-and-dirty sterile room and a pre- and postop holding area. "If you need additional rooms for other purposes, you can use your exam rooms, too," he notes. "That's what we do. On the day of surgery, the whole clinic is converted to a surgery center. We also have a separate laser suite in which we do LASIK, SMILE and PRK. Right now we set aside two days a week for in-office surgery, but we'll be moving to two and a half days soon."

"Both an ASC and an in-office surgical suite are great alternatives for an ophthalmologist, but they make the most sense for different styles and sizes of practices," Dr. Durrie adds. "Generally speaking, an in-office surgical suite is a good option for a practice that can't build an ASC, perhaps because of insufficient volume, or simply has no access to one. In some states Certificate of Need rules prevent a practice from starting an ASC, and this is a good alternative that isn't subject to those rules. It also makes sense for many practices that are just starting up."

—CK

cerned about at all times," he notes. "What reassured me going into this was that there's data on more than 40,000 cases that have been done in an office setting, and that data shows excellent safety. Our track record so far has been excellent as well; although we've only done 92 cases, we haven't had a single instance of endophthalmitis.

"I see a number of reasons for that," he continues, "including the fact that we follow the same protocols as any other OR, and the reality that we can perform the retinal surgery sooner, which lowers risk and is associated with better outcomes. In addition, I know our staff is very well trained, because I trained them myself. I'm not working with someone new, or someone with no retinal surgery experience, which has happened in ASCs and hospitals. And, I always have the equipment I need, which increases the safety of the surgery."

What About Profitability?

Dr. Melendez notes that the financial issues are mixed at the moment. "Our costs are higher when we use the ASC, but the reimbursement is better," he says. "But CMS is now looking at this and considering changing the ruling about office-based surgery to full payment, as they do for ASCs. If that passes, it will become effective in January of 2024. Then you'll see a lot more surgeons thinking about building their own office-based surgery suite."

Dr. Melendez explains that profitability hasn't been a problem for him because he has a premium-lens-oriented practice. "I believe that most doctors who choose to set up an office-based surgery center are trying to offer a more premium experience for patients," he says. "That kind of practice tends to have higher rates of conversion to premium lenses such as Panoptix, Vivity or the Light-adjustable Lens. Combine that with the fact that you're not paying fees to an ASC, and your profitability goes up.

"In addition, we're saving ourselves and our patients time and providing a far better experience," he says. "It's been like night and day for me personally. I used to do 32 cases per day, mostly straight Medicare cases. We had to do high numbers in order to remain profitable. Now I'm doing 12 cases a day, and I have about an 80 percent conversion rate to premium lenses. Today my solution is to do high value, not high volume."

Dr. Feistmann says he realizes that cost is a big concern for most surgeons. "Many surgeons I talk to like the idea of having an OR in their office, but they're worried about the cost and reimbursement questions," he says. "We've just started, so although we have a plan, we don't have a lot of the data about reimbursement yet. But we've gone ahead anyway because it's clearly good for our patients and it eases our stress dramatically when we have to manage an emergency. It's what I would want if I had an eye emergency, instead of having to wait around with oftentimes unnecessary delays, and maybe not ending up in the best operating environment in a late-night situation. Besides, in-office surgery is clearly within our capa-

Study Highlights Role of Emotional Readiness for Cataract Surgery

By Amy Hellem, MLA; Sara LaBelle, PhD; Cynthia Matossian MD, FACS; and Paul Karpecki, OD, FAAO

From the patient's perspective, learning about cataracts and preparing for and undergoing surgery is an emotional journey as much as it is a physical one. With that in mind, it's vital that the cataract care team offer support that promotes comprehensive wellbeing.

As new research indicates, helping patients participate in their care early in the cataract journey can help ensure that they receive timely surgery under improved conditions. Specifically, research shows that when patients are afraid of surgery, they avoid having cataract surgery for as long as possible, enduring poor acuity that could lead to other potential dangers, including falls. However, this same research shows that most patients are willing to engage in a daily ocular surface hygiene routine in the weeks leading up to surgery. This activity gives patients agency as they emotionally adjust to their need for surgery. In addition, by minimizing apprehension, patients may be better prepared to make important decisions about premium surgical options, such as presbyopia and astigmatism correction.

STUDY DETAILS

This noninterventional, cross-sectional investigation of 278 U.S. adults age 65 and older sought to identify cataract surgery candidates' knowledge, beliefs, desires and emotions as well as their behavioral intent to adhere to their doctors' pre-surgical recommendations.[1] In this mixed methods study, two key variables of interest—fear and uncertainty—were measured both quantitatively and qualitatively, providing specific insights into how patients feel so that researchers could extrapolate best practices for mitigating these undesirable emotions.

Specifically, the report, which was recently published in *Clinical Ophthalmology* found that fear is the predominant emotion in one out of every three study participants. Importantly, there is also a notable correlation (r = .44) between fear and intention to delay having surgery for as long as possible. This is potentially troublesome when an ECP tells a patient that they are developing cataracts and that patient silently worries and reacts by putting off future visits until their vision becomes unmanageable. The authors strongly recommend prescribing a pre-surgical prep-kit as a way to combat fear and uncertainty while giving the patient greater agency and autonomy, in effect preparing them both emotionally and physically at a time when they might otherwise avoid proper care and delay surgery.

PATIENT PREFERENCE

There's a common misconception that patients are in a big hurry to have cataract surgery, but this research modifies such reasoning. Specifically, patients who have yet to present for their consult are more likely to be avoiding care. Only 20% of participants in the study said they wanted to have cataract surgery at all and only 8% said they wanted to have cataract surgery as soon as possible.

A second misconception addressed in the study is that cataract surgery candidates are unwilling to participate in a pre-operative prep routine. However, 87% of participants in the study say they would use a pre-surgical prep kit if their doctor gave them one and 83% said they would use a pre-surgical prep kit if they were asked to buy one.

87% of participants in the study say they would use a pre-surgical prep kit if their doctor gave them one.

83% said they would use a pre-surgical prep kit if they were asked to buy one.

IMPLICATIONS

The benefits of a healthy ocular surface prior to cataract surgery are well established, but this is the first study to inquire about the potential emotional benefits of pre-surgical prep. To that end, the authors are initiating future studies to investigate the clinical and emotional outcomes of prep, as well as the impact that initiating a prep routine may have on patient apprehension and intraocular lens selection. Participants will use a moist heat eye compress, lid wipes, and hypochlorous acid solution in the weeks leading up to surgery. As each of these have been shown to improve ocular surface health and limit bacteria, surgeons can offer these conveniently now. Bruder Healthcare makes this easy with its all-in-one prep package that you can recommend to patients in advance of their surgical consultation appointment.

LEARN MORE

[1]Clin Ophthalmol. 2022;16:1003-1008. https://doi.org/10.2147/OPTH.S356895

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OFFICE-BASED SURGERY: ADVERSE SURGICAL EVENTS DATA FROM 37 CENTERS

Surgical events	All patients (18,539 cases)	Patients 65 and older (9,723 cases)
Endophthalmitis	0.027% (5 cases)	0.031% (3 cases)
Unplanned vitrectomy	0.162% (30 cases)	0.237% (21 cases)
Referred to retina	0.070% (13 cases)	0.113% (10 cases)
Return to the OR	0.054% (10 cases) (most for removal of residual cortex)	0.072% (7 cases) (most for removal of residual cortex)
TASS or significant iritis	0.022% (4 cases) (single outbreak at one center)	0.000% (0 cases)
Corneal edema	0.016% (3 cases)	0.021% (2 cases)
Referred to hospital	0.011% (2 cases) (nausea and unable to keep food and fluids down), (previously undiagnosed A. Fib)	0.021% (2 cases) (previously undiagnosed A. Fib)

This represents complete data from 37 centers in which an in-office surgery center was created with help from iOR Partners. Every patient treated in these in-office surgery center was included; the data is collected quarterly as part of each center's Quality Accreditation Program. The average age of all patients was 64.7 years.

bilities, given today's smaller-gauge instruments and reduced need for systemic IV anesthesia.

"The other thing to remember is that profitability isn't just a matter of how much we're paid," he points out. "It's also a question of how much time we spend to earn that payment. I think of it as a ratio, where the numerator is the payment and the denominator is the time I spend on the work. My main goal is to shrink the denominator, meaning taking less time to do an emergency case at the hospital, or avoid taking an entire OR day away from office patients just to do a few surgical cases at the surgery center. This way, even if the numerator (payment) decreases slightly, if the denominator (time) decreases even more, proportionally, I'm actually ahead. And if we can figure out a way to increase the numerator while decreasing the denominator, then we'll be way ahead.

"When I repair a retinal detachment in our office surgical suite, I don't have to wait around until the OR is free," he notes. "In the hospital, it's a huge unknown, and it's stressful and time-consuming. In many cases five hours go by from the time I leave my office for an after-hours emergency until the time I'm done operating in the hospital. If I do that surgery in my office, it takes one hour of my time. So that difference has to be taken into account as well.

"Because we've only recently started doing this, I don't know what the long-term picture will look like," he concludes. "But I know for sure that I'm spending far less time on these cases. I'm leaving the office at 5:30 with the case completed, not leaving the hospital at 10:30 at night."

In-office vs. ASC

"It's clear that some patients haven't been happy with the ambulatory surgery center experience, especially during COVID," says Dr. Melendez. "For example, one advantage of an office-based surgery center is that it's much less crowded. During COVID, patients have wanted to avoid crowds. Furthermore, patients who've had one eye done at an ASC and the other done here tell us it's an entirely different experience. Overall, patients are much happier having their cataract surgery here when they compare the two experiences."

Dr. Melendez points out that scheduling is another big advantage when you're working in your own surgical suite. "We have more control over our schedule, in contrast to an ASC, where you're somewhat dictated to in terms of scheduling," he explains. "Patients get in faster. We can move things around. With office-based surgery, if we want to add a surgery in the afternoon, we can.

"I'm sure folks who own ASCs are concerned about losing some of their volume [because of this trend], but there will always be a need for patients to have surgery in an environment where they have access to IV sedation and general anesthesia," he adds. "Those patients should be done at the surgery center or in a hospital."

"In your own OR, you have full control over everything," Dr. Krajnyk points out. "You can pick whatever lenses and instruments you want. The same technicians who see the patient the day of their appointment see them pre and postop, so patients are much more at ease. The fact that everything is under one roof makes them even more comfortable. And I can tell patients that all of the instruments and tools we're using to do the surgery have been chosen by me, so they'll have a great experience.

"In contrast, I don't have as much control in the hospital or ASC," he says. "I work with a random nurse who doesn't know me. I don't even know which phaco machine or instruments they'll have. The nurse will sometimes give me the wrong instrument; I'll ask for a Sinskey hook and I'll get a 20-ga. needle. And if something goes wrong in the middle of a surgery and you need a piece of equipment right away to prevent a complication from happening, you may find that the nurse has no idea where that piece of equipment is.

"Furthermore, if something breaks, you might have to wait six months or a year for the center to fix it," he continues. "For instance, at a local surgery center they've refused

WHAT ABOUT ANESTHESIA?

Jonathan Feistmann, MD, a retina specialist practicing at NYC Retina in New York City, notes that you can arrange to be able to offer full anesthesia in an office surgical suite. "I know surgeons in some other specialties with in-office ORs who can put patients under general anesthesia," he says. "The reason many don't offer that option—and even some ASCs don't offer it—is because it isn't necessary very often. If you only need this a handful of times during the year, it's not worth all of the things you have to do to make it safe and feasible in this setting. It makes more sense to go to the hospital for those few cases in which it's needed.

"We discussed being able to do general anesthesia in our OR when we were first planning it," he continues. "We decided it wasn't worth the significant amount of effort to make that possible, given that such cases only come up a few times a year. We wanted to build something that could handle the cases that come up on a weekly basis.

"The key, in our experience, is to make it a painless surgery," he adds. "If it's painless, the patients tolerate the surgery very well without the need for systemic anesthesia. We have some patients that require valium prior to surgery, or an MKO melt during surgery for anxiety, but many only need good local anesthesia and reassurance.

"Most office-based surgery centers offer Class A and B anesthesia, which refers to oral and IV sedation," says Robert F. Melendez, MD, MBA, the CEO and founder of the Juliette Eye Institute in Albuquerque, New Mexico. "What a given office-based surgery suite offers depends on their needs and what types of patients they're going to treat. Here, we do oral sedation instead of an IV, and patients find that to be a big relief. We were planning to offer Class B anesthesia as well, but we literally haven't had to do it. If we can see that the patient will need IV sedation, or it's a more complicated case, then we recommend doing the case in the ASC. Generally, I think that's safer for the patient."

—CK

to replace a 30-year-old surgeon's chair that's uncomfortable and no longer rolls. And the WIFI often doesn't work, making it impossible for surgical devices to share information digitally. In my office, if my Zeiss Callisto aberrometer can't get data from my IOLMaster for some reason, I can walk over and get it manually. If that happens in the ASC, it would be a 25-mile drive to get the data.

"We've all been taught to worry about what might happen with no anesthesia to fall back on," he notes. "But the reality is, even in an ASC the anesthesia doesn't always go well. Here, we just give patients a mild oral sedative. They're relaxed and calm, but not zonked out or so loopy that they don't know what's going on. For both the patient and us, that's a win.

"Having our own OR impacts how long things take, as well," he notes. "We can get a cataract patient in and out in less than an hour. If the surgery is done at the hospital or an ASC, it will take at least half a day for the patient."

Dr. Krajnyk adds the patient experience is much nicer in his practice than at an ASC or hospital. "We have LED lighting on the bottom of the walls, and we play light music for the patient. I ask what they want to listen to and we put their choice on Pandora. Patients sit in a massage chair before and after surgery. They don't have to fast overnight, because they're not getting heavy sedation. Their anxiety level goes way down, and they're much happier with the results."

Who Shouldn't be Done In-office?

Some surgeons have pointed out that the vast majority of cataract surgery patients have some comorbidity, theoretically making them poor candidates for in-office surgery. However, Dr. Melendez points out that a co-morbidity, by itself, isn't a reason to avoid office-based surgery. "It's a person with an uncontrolled comorbidity who shouldn't have surgery in the office," he explains. "If your high blood pressure or diabetes is well-controlled, there's no reason you can't have office-based surgery. Plenty of patients with stable hypertension or diabetes have had successful surgery in our office-based OR."

What about claims that up to one-third of cataract patients require anesthesia intervention? "You need to look at that data more carefully," Dr. Melendez suggests. "What does it mean when someone says they needed intervention? Does it mean that they went from oral to IV sedation? That they needed additional IV sedation? And what patient population was being studied? We haven't had to do any anesthesia intervention in our surgery center in nearly 1,000 cases.

"We still sometimes send some patients who have poorly controlled comorbidities such as diabetes, high blood pressure, stroke or heart issues to the hospital or a surgery center," he adds. "Patients who are at high risk should be done in one of those settings. That's why we'd never say that office-based surgery will replace ASCs; we're just saying that for most patients it's a convenient, safe and effective way to do the same surgery that we would do in the surgery center."

"We follow the American Academy of Ophthalmology's guidelines for ambulatory surgery center or hospital admission," Dr. Krajnyk says. "For example, if their blood pressure isn't appropriate, we make them go to their primary doctor or cardiologist to make sure it's under control and ask for clearance for low-risk cataract surgery. If the patient's blood pressure and heart rate are stable, we'll proceed. But if the patient is very frail or fragile, or they're shaking and need general anesthesia, those are patients

we take to the ASC and do under general anesthesia. If the patient has recently had bypass surgery or something like that, we'd just wait four to six months and get cardiac clearance. However, these patients are few and far between.

"People say, 'What happens if there's a medical complication?' The same thing that happens in an ASC," he continues. "You do high-quality CPR, call 911 and the patient is whisked away to a hospital. There's no difference. In reality, anything can happen to anyone at any time. You can walk down the street and get an aneurism. When a colleague asks about this, I ask how many of their patients have had a heart attack on the table. How many have died? Everyone I've ever asked has said 'None.'

"Knowing which patients wouldn't be good candidates isn't as mind-boggling as some people make it sound," he says. "It's no different from 25 years ago when ASCs were starting up. Our patients are generally healthy, and we do a preop evaluation. We check the blood pressure, heart rate, all the things an ASC would do. The protocols are the same.

"For example, one patient drove here from Colorado to have his cataract surgery because his friend had recommended us," he recalls. "On the day of surgery he walked in as if nothing was wrong. He looked fine, said he'd just been in the pool that morning. However, his blood pressure was 190 over 140 with a heart rate of 145. We explained that he was a walking time bomb—he could have died any day! So we had him go to urgent care to get this addressed. At the hospital they put him on three or four medications. A week later he was cleared for the surgery and we did both eyes. Back in Colorado he visited a cardiologist and is doing very well.

"The point is that we're just as capable of catching these things as any other surgery center would be," he says. "They would have done the same thing we did. We have a crash cart with a defibrillator, and everything we need to stabilize a patient, but we haven't actually needed to use it.

"I understand the concern about patient co-morbidities," he concludes. "However, if your patient has a comorbidity, you'd want the patient to be more relaxed and comfortable, because that comorbidity will be less of an issue if the patient isn't nervous and anxious. It's good to give them less sedation and have them be more comfortable and happier, without an IV. In fact, more complications result from anesthesia than from cataract surgery."

> **People say, 'What happens if there's a medical complication?' The same thing that happens in an ASC. You do high-quality CPR, call 911 and the patient is whisked away to a hospital.... When a colleague asks about this, I ask how many of their patiensts have had a heart attack on the table. How many have died? Everyone I've ever asked has said, 'None.'**
>
> ***— Orest Krajnyk, MD***

The Big Picture

"In a hypothetical world, I think if every retina specialist had an operating room in their office, we'd be able to take care of our emergency cases much more easily and quickly," Dr. Feistmann says. "Some people point out that we can't take care of every single patient inside the office, and that's true. But an office-based operating room isn't meant to replace the hospital or ASC; it's meant to add to the tools we have available to us as surgeons.

"At the same time, we've found that we can take care of most emergencies here, far more of them than we anticipated, and we can do so more effectively, comfortably and safely than we expected," he continues. "Although it's only been a short period of time and a small number of patients so far, I'd say that most of the emergency cases we've dealt with have been treatable here in the office surgical suite. For example, the vast majority of my fovea-on retinal detachments have been successfully, safely and comfortably treated in the office. And feedback from the patients about doing the surgery this way has been excellent.

"We've only been using our in-office surgical suite for a short period of time and with a small number of patients, so we're still going very slowly and deliberately," he says. "We're gathering a lot of data, sharing our data with others and working hard to do everything safely. Meanwhile, we still operate in hospitals and surgery centers when the patient's situation requires it.

"We've been pleasantly surprised by a lot of things about this new situation," he adds. "I'm not suggesting that everyone should do this; everyone should do whatever they think is good for their patients. But for us, this has been excellent so far."

"I don't think there could be a better time to consider doing this," adds Dr. Krajnyk. "As we speak, CMS is in negotiations to come up with an approval code for in-office cataract surgery, as well as some glaucoma and retina surgeries."

"This isn't just the wave of the future," says Dr. Melendez. "It's happening now."

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For patients with Graves' disease (GD), Thyroid Eye Disease (TED) may be hiding in plain sight.[1,2]

Up to 50% of patients with GD may develop TED, a separate and distinct disease which can progress if left untreated. Look out for the early signs and symptoms[3-7]:

- **Proptosis**[1]
- **Diplopia**[3]
- **Dry eyes**[8-11]
- **Sensitivity to light**[12]
- **Grittiness**[8-11]
- **Pain or pressure behind the eyes**[1,13]

If you identify new or changing signs or symptoms, consult with an eye doctor who specializes in TED right away.[1,14]

Visit TEDimpact.com to find a TED specialist or contact a Horizon Representative at 1-855-950-2076.

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HORIZON

OPTIMIZING YOUR OCT

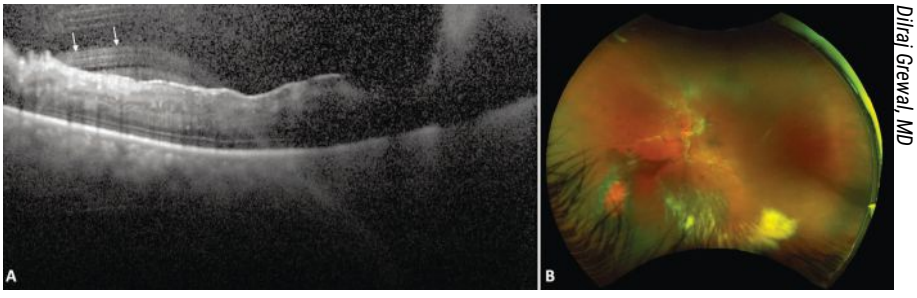
Experts share their tips for interpreting your OCT results and avoiding artifacts.

LIZ HUNTER
SENIOR EDITOR

Technology can sometimes be a polarizing topic in health care. While many advancements have led to improved patient outcomes, there are also those that have introduced a new set of obstacles for physicians to overcome. Some technologies can even fit into both of these camps.

Take optical coherence tomography. Few ophthalmologists would argue its impact on the field. In its approximately three-decade existence, OCT has opened a window into the diagnosis and treatment of retinal and anterior segment diseases, and its continued evolution with the development of optical coherence tomographic angiography will likely only get better. However, OCT is not without its limitations, the most common of which are image artifacts. These artifacts can influence how data are interpreted and possibly make your determinations inaccurate.

We spoke with retina specialists about how to spot artifacts and what steps to take to reduce them.



Dilraj Grewal, MD

Figure 1. Image artifact resulting in degraded OCT image due to vitreous hemorrhage in an eye with proliferative diabetic retinopathy. OCT (A) shows artifactual hyperreflective streaks in the vitreous (white arrows) and poor image quality due to the shadowing caused by the vitreous hemorrhage in the right half of the image resulting in poor visualization of the retinal layers. Fundus photograph (B) shows proliferative diabetic retinopathy with an old vitreous hemorrhage.

A Closer Look

Dilraj Grewal, MD, an ophthalmologist and retinal surgeon at Duke Eye Health in North Carolina, agrees that OCT has transformed the field of ophthalmology. "OCT is an essential component of our modern ocular exam. In fact, we can also consider it an ocular vital sign. For retinal patients, it's an integral and indispensable part of evaluation and decision-making," he says.

Keeping in mind how important OCT is, Dr. Grewal doesn't take any scan at face value. "As with any kind of imaging modality, it's very important to consider scan quality as an integral component of your decision-making because what you see is what you get. If your inputs aren't accurate, which are impacted by scan quality, then your outputs or treatment decisions may not be accurate either," he advises.

Nadia Waheed, MD, MPH, an associate professor at the Tufts University School of Medicine in Boston, says OCT provides incredibly dense information, with various forms of data output: linear (B) scans, through

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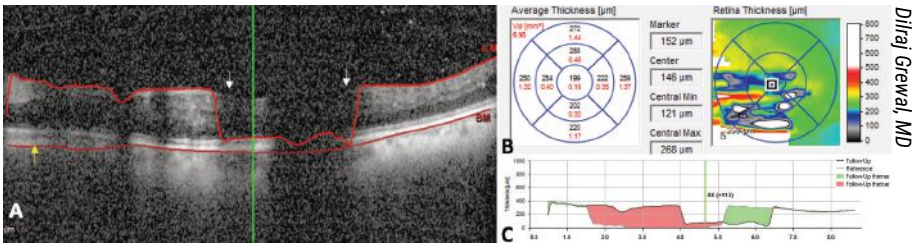
the area of interest/fovea; and volumetric scans, obtained through raster or cross-scanning of the macula. The information presented can be qualitative, i.e., identifying retinal pathologies; or quantitative, e.g., calculating retinal thickness.[1]

"OCT devices can acquire line scans, which are multiple acquisitions at exactly the same area. You then average those acquisitions to get better visualization," Dr. Waheed says. "The other output is the macular cube scan, which takes multiple images of adjacent areas, most commonly centered on the fovea. When you're interpreting OCT qualitatively, it's really important to look at the entire cube and not just one picture from the cube, because then you could easily miss things."

Lisa Olmos de Koo, MD, MBA, associate professor of ophthalmology in the vitreoretinal surgery division at the University of Washington in Seattle, finds the cube scan provides the most useful information, as opposed to the map. "I do think it's important to look at the map, but a map is only a map because of segmentation lines that usually a computer creates of the different layers," she says. "If there's any kind of decreased signal strength or an artifact, that segmentation can be off and you can't trust it, impacting things such as calculation of thickness in various quadrants. Those are all helpful only if the segmentation is accurate, so I look at those segments secondarily."

As OCT devices evolve, Dr. Waheed says surgeons are seeing more. "Not only can we characterize disease better, but it can also be a prognostic tool," she says. "As we get higher resolution and faster speeds, we can better visualize the retina overall and see things that may be harder to detect when you just look at the traditional cross-sectional images."

But even as technology takes us deeper into the retina, surgeons have to be aware of what they're looking at, says Dr. Grewal, and whether it represents true anatomy or pathology versus a potential artifact.



Dilraj Grewal, MD

Figure 2. Error in segmentation (A) due to failure of the algorithm to correctly identify the internal limiting membrane (white arrows) and Bruch's membrane (yellow arrow). The resulting thickness maps that are generated are erroneous (B) and thickness change maps in such situations (C) compared to the prior scans aren't accurate reflections of change in retinal thickness and shouldn't be used to make treatment decisions.

"It comes down to how we use OCT in the assessment of patients. We use it both qualitatively and quantitatively," he says. "For qualitative assessment, we can visualize different layers of the retina and vitreous down to the choroid and visualize the normal structure or variations of abnormalities on it. So, if there are artifacts in the image, that's going to impact our qualitative assessment. For example, the image may appear to be very grainy, with a lot of white dots in the vitreous. One might interpret that as inflammation or the presence of blood in the vitreous, whereas the reality is that it may just be an artifact due to poor scan quality."

Identifying and Rectifying Artifacts

Artifacts can be caused by several factors, including the patient, the device or software and the operator/imager.

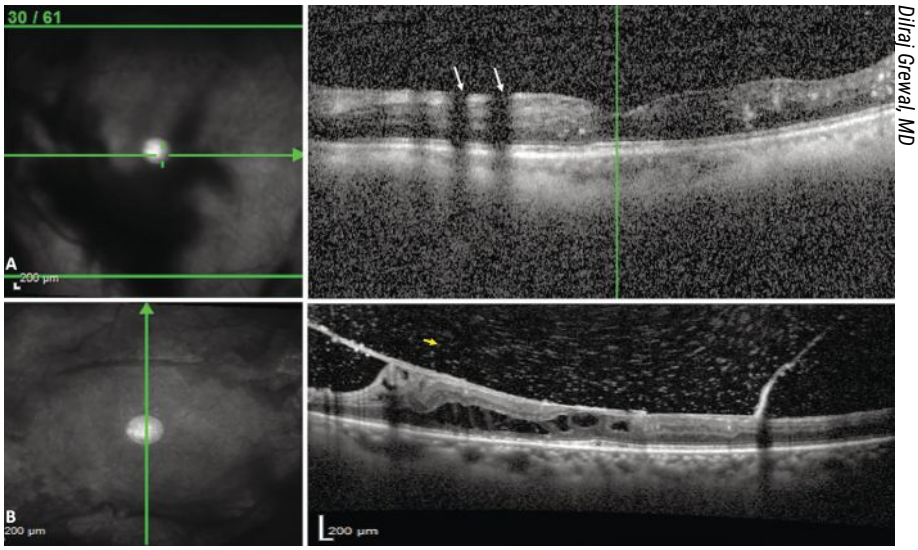
Motion artifact is one of the most common issues caused by the patient, says Dr. Waheed. "If the acquisition is long, patients can move and you get a lot of artifacts because of motion," she says. These artifacts can result in segmentation errors and potentially appear as abnormalities in the retinal nerve fiber layer thickness measurement.[1]

Unless recognized, this artifact could severely alter your treatment plan, says Dr. Grewal. "If there's a motion artifact, then you may get irregular variations in the anatomy, which is again, an artifact causing a qualitative error of assessment rather than true pathology," he says. "And in terms of quantification, any issue with scan quality may affect the segmentation of the retinal layers by the software.

"Measuring the thickness of different layers depends on accurate segmentation of the boundaries, so if these boundaries are erroneously depicted due to quality issues, then your quantitative measurements are going to be erroneous as well," Dr. Grewal continues. "This has significant implications because you may, for example, be monitoring central subfield thickness (the thickness of the retina in the central one millimeter circle). If you're using that to make treatment decisions, scan quality issues or artifacts may cause that value to be erroneously high or low, and that would impact your treatment decision. So, it's very important to pay attention to the quality of the image prior to interpreting it whether qualitatively or quantitatively."

Motion artifacts may be due to the patient's inability to fixate, which depends on their vision, Dr. Grewal notes. "If they're not able to fixate on the scan pattern—because any image that's acquired is based on a particular scan pattern that the machine projects, whether it's a raster, radial or circle scan—if the patient can't track and follow during the scan, then the scan may be off the foveal center and there's potential for the scan to have significant motion artifact," he says.

Motion artifact can be prevented



Dilraj Grewal, MD

Figure 3. Vitreous opacities causing a shadow artifact (A, white arrows). The white dots seen in the vitreous are due to poor image quality and aren't true vitreous hyperreflective dots, which are seen in B, in a good quality OCT scan (yellow arrow).

with clear instructions, a fixation pointer and artificial tears, advises Dr. Waheed.

Fortunately, evolving technology is contributing to reducing motion artifacts. "As scan acquisition time goes down, blinking (motion) doesn't matter as much because you can get more of a scan before the patient feels they have to blink or move," says Dr. Olmos de Koo.

The eye's condition will also contribute to scan quality issues, says Dr. Grewal. "These issues may start all the way from the corneal tear film," he says. "If the cornea is very dry, or there's corneal edema, then it's going to impact the penetration and reflectance of the light beam, which is what OCT is based on. This will hold true for any structure as you go inward."

"Rectifying a poor tear film or dry corneal surface is among the simplest issues to resolve," Dr. Grewal continues. "Instilling artificial tears and asking the patient to blink frequently, as well as performing OCT early in the evaluation process as the patient gets worked up, are some of the strategies that can be used to mitigate the effects of poor scan quality due to the tear film."

Artifacts are also connected to the devices themselves. "There are some issues inherent to the device and the software that lead to limitations of the technology," notes Dr. Grewal. "These may include the field of view or the ability to visualize the peripheral retina, and issues with the software segmentation algorithm, where there may be failure of segmentation due to the software's inability to detect the boundaries in the presence of significantly distorted anatomy."

Misidentification of the retinal layers carries certain implications, with outer retinal layer misidentification being more significant. Srinivas R. Sadda, MD, of the Doheny Eye Institute in Los Angeles, reported errors in thickness measurement and retinal boundary detection in 92 percent of eyes[2] undergoing Stratus OCT imaging. This was most severe in only 13.5 percent of eyes; it was attributed to a higher FCTSD-to-FCT ratio, as well as the presence of subretinal fluid.

Segmentation errors have been a significant issue, although they're getting less problematic because the software works really well, says Dr. Waheed. "For instance, if you have outer retina line misidentification, that line is used to quantify how thick the retina is. And it's important in quantifying, for example, if there's fluid there and you're using the quantification to make decisions about therapy. So if you have outer retinal misidentification—and this often happens in patients who have outer retinal disease like macular degeneration—then the quantification is inaccurate. Retina thickness is really important in a patient with macular degeneration or diabetic macular edema."

This demonstrates the role pathology plays in artifacts. Dr. Olmos de Koo hesitates to connect any particular artifact to any machine, but says she wouldn't be surprised if different depths of penetration lead to different artifacts. "There's extended depth imaging, EDI, and there's standard imaging. You might be more interested in the vitreoretinal interface, in which case you wouldn't want to do EDI," she says. "But when you need to focus on the choroid, EDI can give you a clearer picture of what's below the retina and how it may impact retinal disease. In certain cases you can't have it all and it's best to focus your acquisition of images on the specific pathology that you're looking at."

Segmentation artifacts can be subtle, says Dr. Grewal. "Segmentation can be inaccurate either because of a focal scan quality like the shadow artifact from vitreous opacity, or because of focal areas of poor signal strength that could cause dropout of signal and therefore poorly resolved delineation of the retinal boundaries," he says. "It's often very helpful to look at the thickness maps to see if there are focal areas where there are irregularities, because you would typically expect the thickness map to be relatively smooth, following normal retinal anatomy with a foveal dip. If you're seeing large variations, such as an inordinate variations in thickness in one area that don't correlate with what you're seeing on your exam, that should prompt you to determine why the thickness is affected, particularly if you're using those values to make treatment decisions. That includes assessing whether you know there's an epiretinal membrane or vitreomacular

traction, or the layers haven't been correctly segmented.

"The posterior hyaloid or the posterior boundary of the vitreous are hyper-reflective, the machine algorithm may recognize that as an internal limiting membrane, and therefore the thickness of the retina is going to be artificially increased," Dr. Grewal continues. "When a patient presents with a very long eye, you may get some images where the scans may be flipped over or clipped. This is because the way OCT works is that there's a certain scan width within which the OCT signal is going to be of the highest quality. If the eye is very long with a posterior staphyloma, then the scan may be flipped outside these limits and that'll cause an artifact."

In neovascular conditions such as diabetic retinopathy or macular degeneration, the presence of hemorrhage may cause scan quality issues. Dr. Grewal says, "If there's a large submacular bleed in macular degeneration, then the penetration into the retina will be impacted due to the hyperreflective blood. If there's a bleed in diabetic retinopathy, then your signal strength into the retina is going to be impacted.

> **"It's very helpful to have a checklist in terms of scan quality, looking for motion artifact, registration to the baseline scan, shadow artifact and whether the images are clipped."**
> ***— Dilraj Grewal, MD***

"Some other factors that may cause such an impact include the presence of significant inflammation or blood in the anterior chamber, posterior synechiae in the iris, cataract and vitreous haze, blood or opacities in the vitreous cavity," Dr. Grewal continues. "Some strategies may help to overcome the vitreous opacities and vitreous floaters for example—you can ask the patient to look around just prior to image acquisition—but that is again contingent on the opacities not being very dense."

Another artifact found only in SD-OCT is the mirror artifact. "SD-OCT machines generate two OCT images which are symmetric around the zero-delay line," Dr. Waheed explains. "If the retinal image crosses the zero-delay line anteriorly, the corresponding symmetric mirror image on the truncated side will cross into the scanning range and be seen as a 'ghost' mirror

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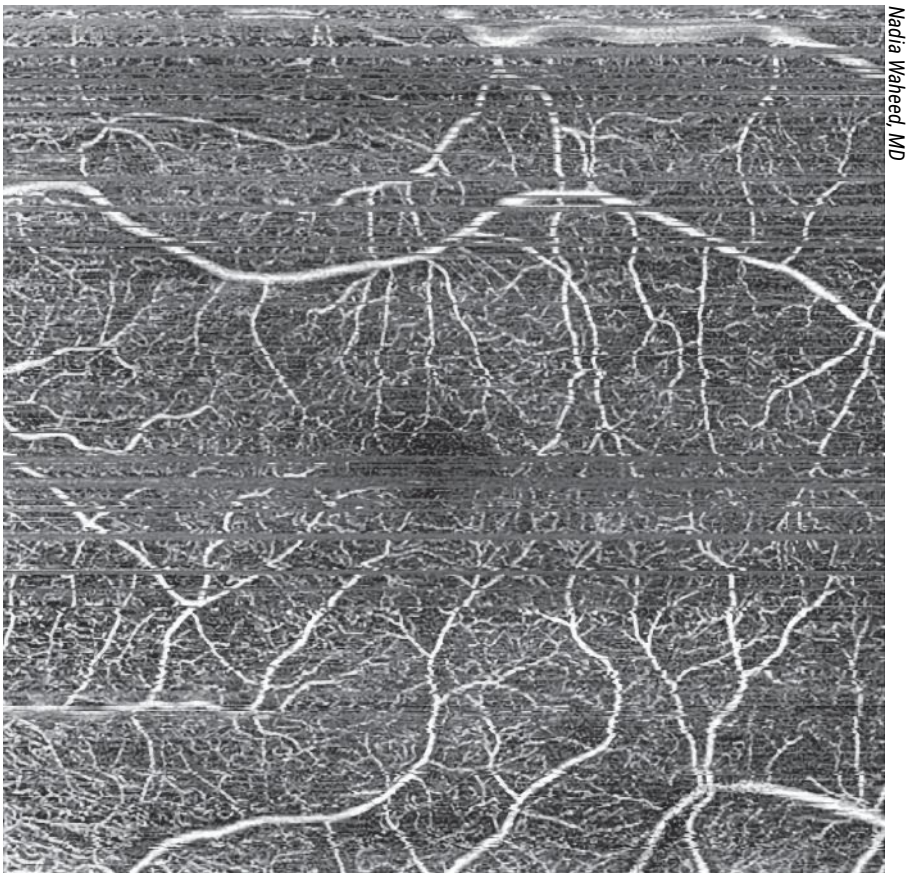

Nadia Waheed, MD

Figure 4. An example of motion artifact (horizontal lines mainly seen in the upper third and center of the image) on a patient with diabetic retinopathy.

image. This artifact can be corrected by properly positioning the retina to avoid crossing the zero-delay line."

Mirror artifacts happen frequently in myopic eyes, adds Dr. Olmos de Koo. "When you have a very highly curved eye, let's say you have a myopic contour, and it's very U-shaped, it can actually flip and make the retina look like it's upside down," she says. "This happens frequently in very myopic eyes, making those harder to image. When that happens, it's very clear that it's an artifact—you're not going to mistake it for another disease. But those OCTs are harder to evaluate."

Dr. Waheed says mirror artifacts can also occur in cases of massive retinal thickening, poor scan placement or elevation of retina due to RD, schisis or tumor.

Dr. Olmos de Koo says acquiring OCTs from challenging patients requires a lot of skill. "Experienced photographers are gems," she says. To ensure her photographers obtain the best scan possible, she offers these tips: "I try to make sure the scans are centered on the fovea and capture the foveal center, and that they register to the prior scan for comparison," she explains. "The person doing the scan also needs to make sure that the ocular surface is well-lubricated, so I keep a supply of artificial tears next to the machine. If there's any concern at all, I encourage them to apply tears and reacquire the scan."

Dr. Grewal agrees that technicians play a part in mitigating some factors. "In follow-up visits, it's important to remember to register the follow-up images to the baseline image so that measurements are accurately compared, and to ensure that the same area of the retina is being scanned," he says. "This is particularly important when the anatomy is distorted. If your normal foveal contour is lost in the presence of significant edema or scar tissue on the retina, and you're not scanning the exact same area over time, then you may again get erroneous comparisons to baseline."

Finally, the retina specialist must also take an active role in OCT accuracy. Dr. Grewal relies on a mental checklist. "It's very helpful to have a checklist in terms of scan quality, looking for motion artifact, registration to the baseline scan, shadow artifact and whether the images are clipped," he advises. "Also, have a defined scan protocol for your patients so that the potential variations are reduced as you go through your workflow."

Often, doctors need to accept that some artifacts are simply unavoidable, explains Dr. Olmos de Koo. "You can get a lot of information from an ocular OCT. You just need to optimize your image acquisition and recognize the limitation of any artifacts, remembering that you can still get useful information even when there are artifacts," she says. "With blink artifact or motion artifact, that'll just give you poor signal strength or cause you to be unable to acquire a cube. Sometimes you only get a line scan—but you can get better resolution with just a line scan, rather than doing a whole cube or raster scan. And if that's all you can get because of motion or blink or poor media, then you take that and go with it. You shouldn't just discount the whole scan because there are some artifacts." ◀

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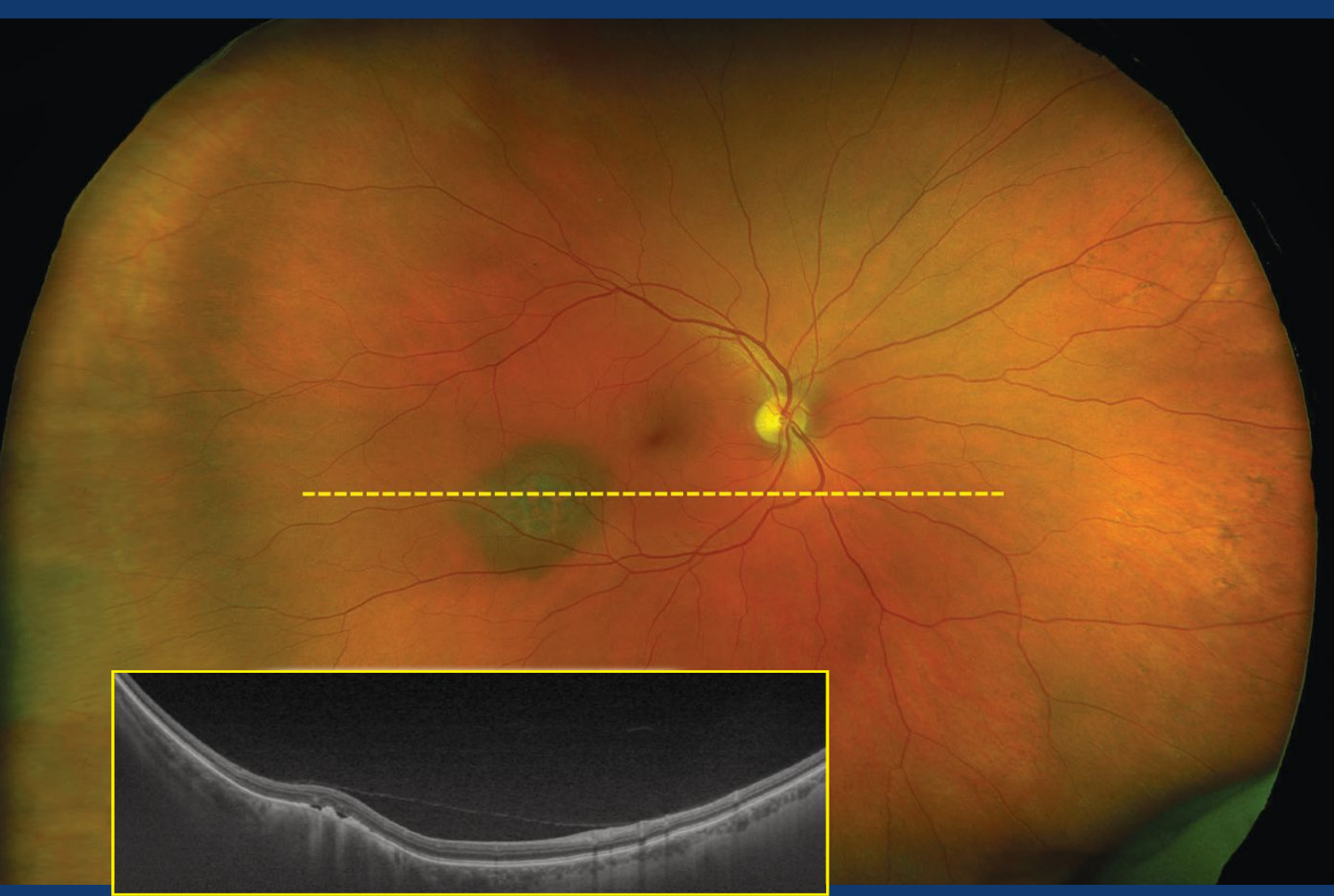

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1. Successful interventions to improve efficiency and reduce patient visit duration in a retina practice; Retina, 2021. 2. Comparison of image-assisted versus traditional fundus examination; Eye and Brain, 2013. 3. The Impact of Ultra-widefield Retinal Imaging on Practice Efficiency; US Ophthalmic Review, 2017.

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A Classification System For Uveal Melanoma

Learn more about this new, reliable tool for predicting disease severity and prognostic outcomes.

KEVIN R. CARD, BS, ELENI KONSTANTINOU, MD, AND CAROL SHIELDS, MD
PHILADELPHIA

As an ophthalmologist, you're often on the front line when it comes to diagnosing a patient with uveal melanoma. When this diagnosis is made, it's often accompanied by a flood of questions from the patient, such as: What's the prognosis? Did it spread anywhere else? For years, ophthalmologists have relied on UM classification systems to help answer these questions. Recently, a new classification system, The Cancer Genome Atlas, was developed, and bases its classifications on a tumor's genetic profile. Here, we present an overview of the genetic aberrations that define this classification system, as well as a review of the literature for outcomes in patients with uveal melanoma stratified by this system.

Classifying Uveal Melanoma

Uveal melanoma, the most common primary intraocular malignancy in adults, is a malignant neoplasm affecting the iris, ciliary body and choroid.[1] While these tumors can be visually threatening, they also carry a significant risk for metastatic disease with the most common sites being the liver, lung, bone and skin, respectively.[2] As mentioned earlier, ophthalmologists are usually the first to diagnose UM and refer a patient to an ocular oncologist. Making an accurate prognosis and determining the risks for systemic metastasis depends in large part on tumor size, location, genetics and classification.[3]

There are a few classification systems for UM that aid in the prediction of prognosis. These systems have taken into consideration the anatomic features of the tumor and/or genetic aberrations characterizing the tumor.[3-9] The American Joint Committee on Cancer Classification 8th edition criteria separated UM into categories and stages based on the tumor anatomy, with a focus on involvement of the choroid and ciliary body, basal dimension and thickness of the tumor, distance to the foveola, any documentation of tumor growth and evidence for extraocular extension.[3]

The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA) classification is the result of an international collaboration led by the National Cancer Institute Center for Cancer Genomics and the National Human Genome Research Institute in 2005. TCGA project's mission was to characterize the molecular changes that occur in cancer cells by analyzing data collected from thousands of human samples. All told, TCGA collected and analyzed over 20,000 tissue samples from 33 cancer types (including those specific to uveal melanoma) to elucidate not only the genes that play a role in each type of cancer, but also identify protein-complexes and pathways that contribute to these malignancies.[10-12] This analysis led to refined systems of grouping for various cancers, allowing treatment plans to be modified to address the clinical, histopathologic, and now genetic, alterations in cancer types. More than

TABLE 1. THE CANCER GENOME ATLAS (TCGA) CLASSIFICATION SYSTEM OF UVEAL MELANOMA CLASSES A, B, C, AND D BASED ON GENETIC MUTATIONS

Characteristic Genetic Aberrations per TCGA Class	TCGA A	TCGA B	TCGA C	TCGA D
Chromosome 3	Disomy 3	Disomy 3	Monosomy 3	Monosomy 3
Chromosome 8	Normal 8q	8q gain	8q gain	8q gain (multiple)
Significantly mutated genes	*EIF1AX*	*SF3B1*	*BAP1*	*BAP1*
Prognosis	Favorable	Late metastasis	Unfavorable	Unfavorable

Abbreviations: EIF1AX, Eukaryotic Translation Initiation Factor 1A X-Linked; SF3B1, Splicing Factor 3b Subunit 1; BAP1, BRCA1 Associated Protein 1
Adapted from: Robertson AG, Shih J, Yau C, et al. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. Cancer Cell. 2017;32:2:204-220; Jager MJ, Brouwer NJ, Esmaeli B. The Cancer Genome Atlas Project: An integrated molecular view of uveal melanoma. Ophthalmology 2018;125:8:1139e1142.

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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.

2.5 petabytes (2.5 million gigabytes) of data relating to the genetic and proteomic characteristics of these cancers have been generated by this analysis.[13]

The TCGA researchers identified a multitude of genetic, histologic, immune and proteomic influences in uveal melanoma which contribute to the disease's prognosis.[11] Based on their findings, the researchers[11,12] synthesized a classification system that stratifies uveal melanoma into four groups: TCGA Group A *(Figure 1A)*; TCGA Group B *(Figure 1B)*; TCGA Group C *(Figure 1C)*; and TCGA Group D *(Figure 1D)*. Each TCGA group reliably characterizes uveal melanomas by severity of disease and risk for metastasis *(Table 1)*.[12]

TCGA Findings in Uveal Melanoma

In 2017, A. Gordon Robertson, PhD, and co-workers at Vancouver's Michael Smith Genome Sciences Centre first published TCGA data in the Rare Tumor Project collected from 80 human eyes with UM and extrapolated on the relevant genetic pathways involved. The researchers found four molecular and clinical distinct subsets of UM.[11] A year later, The Netherlands' Martine J. Jager, MD, and colleagues simplified the findings and proposed the four-category classification system of UM that's been implemented clinically to predict prognostic characteristics of the disease, such as rate of metastasis and death.[12] The four categories each differ genetically based on chromosome 3 and 8 findings.[11,12] This classification system has since been documented to be more accurate than the AJCC 8th edition regarding its use in prediction of five-year rate of metastasis.[3]

TCGA explored numerous alterations in DNA, RNA expression, protein translation, methylation status and immunologic factors, and ultimately identified four clinically relevant subtypes of UM, each with distinct genetic aberrations and prognostic characteristics. These genetic mutations not only correlated with clinical outcomes of UM, but they were mutations specifically not found in cutaneous melanoma. The primary factor in deciding prognostic outcomes is the status of chromosome 3: Disomy 3 (D3) showed favorable prognosis while monosomy 3 (M3) showed unfavorable prognosis. Within each grouping of D3 and M3 were additional stratifications decided by absence or presence of functional gains in 8q.[11]

Among the D3 tumors, Dr. Robertson identified two genetic aberrations—nearly mutually exclusive—that contributed to tumor pathogenesis. Mutations in EIF1AX were identified in uveal melanomas that were characterized by chromosome 3 disomy and no gains in 8q (D3, no 8q gain).[11] Mutations in SF3B1 were also identified in disomy 3 tumors, but only if they had partial functional gains in 8q (D3, partial 8q gain). These two D3 tumor types had distinct somatic copy number alterations from one another, leading to D3 tumors being subclassified into tumors with D3 and no 8q gain and tumors with D3 and 8q gain *(Table 1)*.[11]

The UMs which showed M3 demonstrated loss of function of tumor suppression gene BAP-1 (located on 3p21). Tumors with this genetic aberration were followed by a global DNA methylation state and were highly correlated with UM metastasis. Even though the global methylation state was shown to be shared among all M3 tumors, the authors identified differences in cell signaling pathways and protein expression as well as differences in clinical outcomes between M3 tumors without multiple 8q gains (M3, 8q gain) and the M3 tumors with multiple 8q gains (M3, multiple 8q gains). Tumors with multiple 8q gains showed evidence of presence of 8q isochromosomes (chromosome 8 with 2 q arms) *(Table 1)*.[11]

Based on the findings of Dr. Robertson's group, Dr. Jager and her colleagues proposed TCGA Group A (D3, no 8q gain), TCGA Group B (D3, partial 8q gain) TCGA Group C (M3, 8q gain), and TCGA Group D (M3, multiple 8q gains).[11,12] This classification system has been widely used clinically, and has been the basis for important validation studies and studies focused on the multitude of clinical correlations and implications of this classification system.[1,14,15] Moreover, TCGA's classification system has been shown to improve the level of predictive precision compared to the previously dominant American Joint Committee on Cancer classification system when both TCGA and AJCC criteria were taken into consideration.[16]

The Current Literature on TCGA and UM

Since the publication of the TCGA's classification system, efforts to apply the system clinically have revealed a great deal about patient prognosis in patients in increasing TCGA categories (A vs. B vs. C vs. D). In 2019, a group of researchers was the first to apply the TCGA classification clinically to a cohort of 658 patients with UM, primarily focusing on the difference in rates of metastasis and death at five years.[1] In this cohort, the researchers found that not only did the rate of metastasis increase with increasing TCGA group (3 vs. 10 vs. 25 vs. 41 percent, respectively; $p<0.001$), but the mean time to metastasis decreased with increasing TCGA group (42.1 vs. 41 vs. 30.8 vs. 21.1 months, respectively; $p<0.001$).

When types of metastasis were analyzed individually, the rates of metastasis similarly increased with increasing TCGA grouping with statistical significance. This was shown for liver metastasis (2 vs. 10 vs. 24 vs. 40 percent, respectively; $p<0.001$), lung metastasis (<1 vs. 1 vs. 3 vs. 7 percent, respectively; $p<0.001$), as well as a grouping of other types of metastasis, including bone, brain, breast, intestine, distant lymph nodes, mesentery, muscle and skin (1 vs. 3 vs. 3 vs. 9 percent,

respectively; p=0.001). Other statistically significant associations with increasing TCGA grouping were also described, including lower visual acuity, more anterior tumor location, lower frequency of tumor epicenter in the choroid, greater distance from the optic nerve and foveola, greater basal diameter and greater tumor thickness as TCGA group increased.[1]

One of this article's authors, Carol Shields, MD, and her group then performed a follow-up study to further validate these findings on a cohort of 1,001 eyes with a follow-up period of 10 years.[14] Unsurprisingly, this study confirmed an increasing rate of metastasis with increasing TCGA classification (3 vs. 9 vs. 20, vs. 46 percent, respectively; p<0.001) as well as decreased time interval to metastasis (37.4 vs. 38.7 vs. 27.7 vs. 21.5 months, respectively; p=0.009).

The rates of individual types of metastasis similarly increased with increased TCGA grouping. This was shown in liver metastasis (2 vs. 9 vs. 20 vs. 46 percent, respectively; p<0.001), lung metastasis (<1 vs. 1 vs. 4 vs. 10 percent, respectively; p<0.001), and other metastasis (1 vs. 4 vs. 5 vs. 14 percent, respectively; p<0.001).

Dr. Shields' group also found that the rates of melanoma-related death increased with increasing TCGA category (<1 vs. 0 vs. 2 vs. 7 percent, respectively; p=0.003). Kaplan Meier analysis of this cohort demonstrated increasing metastasis rates at the five-year mark (4, 12, 33, and 60 percent, respectively; p<0.001) as well as the 10-year mark (6, 20 and 49 [data on the last category isn't available], respectively; p<0.001).[14] This data has been very helpful for counseling patients, managing their expectations and coordinating their treatment *(Table 2)*.

A collaboration between Wills Eye Hospital and Leiden University Medical Center in the Netherlands then explored the impact of TCGA grouping on patient outcomes based on iris color; lighter iris color (blue, gray, and green irides) has been shown to be an independent factor increasing the risk for development of UM compared to darker irises.[15] They found that although there was no difference in mortality when stratified by iris color (p=0.28), the chromosome 3 and 8q copy numbers made a greater impact on survival in patients with lighter irides (gray, blue, and green) as well as in patients with lightly pigmented tumors.

Chromosome 3 status impacted patient survival in blue-iris (p=0.001) and green-iris patients (p<0.0001), but not in brown-iris patients (p=0.43). The same was found to be true for the impact of 8q status in blue-iris (p=0.001) and green-iris patients (p<0.001) when compared to its effect on survival in brown-iris patients (p=0.28). They concluded that iris pigmentation likely plays a role in the oncogenic behavior of UM tumors and that iris color shouldn't be overlooked when assessing patients with UM.[15]

Efforts to further refine this system of UM classification have taken into account the system that TCGA seemed to be replacing, the AJCC. Unlike the TCGA criteria, AJCC criteria include clinical factors of the tumor, such as tumor size, ciliary body involvement and extrascleral extension.[3] A group at Leiden University Medical Center led by Maria Chiara Gelmi, MD, found that combining the AJCC with the TCGA criteria provided a refined system with increased prognostic accuracy compared to either system

TABLE 2. 5-YEAR AND 10-YEAR KAPLAN MEIER ANALYSIS OF METASTASIS AND DEATH OUTCOMES IN UVEAL MELANOMA BASED ON THE CANCER GENOME ATLAS (TCGA) CLASSIFICATION SYSTEM

5-year and 10-year Outcomes by TCGA Class	TCGA A	TCGA B	TCGA C	TCGA D	p-value
Incidence of Any Metastasis					
5-year incidence of any metastasis (%)	4	12	33	60	<0.001
10-year incidence of any metastasis (%)	6	20	49	Not available	<0.001
Incidence of Liver Metastasis					
5-year incidence of liver metastasis (%)	2	12	33	58	<0.001
10-year incidence of liver metastasis (%)	4	20	45	Not available	<0.001
Incidence of Lung Metastasis					
5-year incidence of lung metastasis (%)	1	1	7	24	<0.001
10-year incidence of lung metastasis (%)	1	5	11	Not available	<0.001
Incidence of Metastasis Elsewhere*					
5-year incidence of metastasis elsewhere* (%)	2	5	12	29	<0.001
10-year incidence of metastasis elsewhere* (%)	3	10	17	Not available	<0.001
Incidence of Death					
5-year incidence of death (%)	<1	0	7	15	<0.001
10-year incidence of death (%)	1	0	7	Not available	<0.001

Adapted from: Shields CL, Mayro EL, Bas Z, et al. Ten-year outcomes of uveal melanoma based on The Cancer Genome Atlas (TCGA) classification in 1001 cases. Indian J Ophthalmol 2021;69:1839-45.
*Metastasis elsewhere includes metastasis to bone, brain, breast, intestine, distant lymph nodes, mesentery, muscle and skin.

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alone. They essentially found that chromosomal aberrations had a greater impact on AJCC stage II and III tumors compared to AJCC stage I tumors. They also found mutually exclusive prognostic differences in TCGA groups C and D that were further subclassified into AJCC stage II and stage III. Thus, they concluded that TCGA C patients should also have clinical factors such as tumor size, involvement of the ciliary body and extrascleral extension (all predictive of a poorer prognosis) taken into consideration. They also found that chromosome status should be taken into account when estimating a prognosis with tumors staged as AJCC II or III.[16]

Subsequently, Viktor Gill, MD, PhD, and colleagues at the Department of Pathology, Västmanland Hospital in Västerås, Sweden, expanded on the idea that genetic and clinical factors that hold predictive value independent of the genetic status should be combined when categorizing patients with UM.[17] They explored the combination of clinical and genetic prognostic factors in 1,796 patients with UM from Wills Eye Hospital and St. Erik Eye Hospital in Stockholm.[17] A multivariate Cox regression model determined that male sex, patient age at diagnosis, AJCC T category, monosomy 3 and tumor involvement in the ciliary body were all independent predictors of metastasis. Using this data, they constructed and validated a point system (0-12.5) within their patient cohort. Points were assigned as follows when 8q data was available:

- 0.5 points for male sex;
- 0.5 points for age over 70 years;
- 0.5 points for ciliary body involvement;
- 1.5 points for extrascleral extension of ≤5mm;
- 3 points for extrascleral extension >5mm;
- 2 points for monosomy 3;
- 1 point for 3 copies of 8q;
- 2 points for >3 copies of 8q;
- 1 point for AJCC-T category 1;
- 2 points for AJCC-T category 2;
- 3 points for AJCC-T category 3; and
- 4 points for AJCC-T category 4.

The resulting total determines whether the patient belongs to prognostic group 1 (2 points or fewer), prognostic group 2 (2.5 to 4.5 points), prognostic group 3 (5 to 7 points), or prognostic group 4 (7.5 points and up). Their univariate and multivariate regression models suggested a more accurate predictability of mortality related to UM than AJCC or TCGA individually.[17]

In summary, TCGA's classification system has provided a highly reliable and applicable prognostication system for patients with UM, guiding expectations for morbidity and mortality as well as approaches to treatment and coordinated systemic monitoring. The system has been widely used in ocular oncology and serves as a reliable point of reference for projects aiming at improving how UM is categorized.

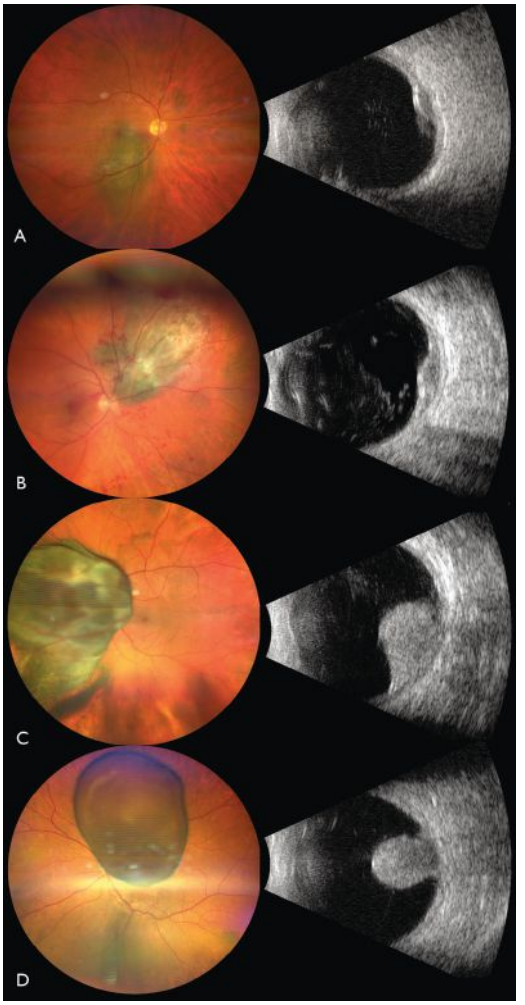

Figure 1. The Cancer Genome Atlas classification of uveal melanoma using fine needle aspiration biopsy. (A) TCGA Group A UM, measuring 11 mm x 7 mm in base with shallow subretinal fluid and orange pigment (left panel) and ultrasound showing an acoustically-hollow tumor with thickness of 3.1 mm (right panel). (B) TCGA Group B UM, measuring 12 mm x 11 mm in base with shallow subretinal fluid (left panel) and ultrasound showing an acoustically-hollow tumor with a thickness of 3.9 mm (right panel). (C) TCGA Group C UM overhanging the optic disc, measuring 18 mm x 17 mm in base with shallow subretinal fluid (left panel) and ultrasound showing a mushroom-shaped tumor with thickness of 10.7 mm (right panel). (D) TCGA Group D UM overhanging the optic disc, measuring 14 mm x 10 mm in base with shallow subretinal fluid and overlying retinal invasion (left panel) and ultrasound showing a mushroom-shaped tumor with thickness of 10.3 mm (right panel).

Overall, there's definite value in taking patient genetics and clinical data into account when caring for UM patients. Further research on larger patient cohorts may be done to determine more exactly the effect each individual factor has on a patient's prognosis. ◀

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(Continued on p. 76)

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Better Ways to Manage Patient Flow

One surgeon shares strategies he's used to ensure more timely movement through the office—and happier patients.

HUSAM ANSARI, MD, PHD
BOSTON

As reimbursement for our services continues to shrink and the number of patients needing our help continues to rise, all of us find ourselves dealing with a crush of patients moving through our offices. This can leave us struggling to maintain the quality of care we provide. Meanwhile, the result can be long waiting times and frustrated and angry patients. For many years, that was the situation in my practice. My patients took a long time to get through their appointments because of the number of patients in the office and bottlenecks that arose in our patient flow. As a result, I had many chronically unhappy patients.

Eventually, I decided to take the bull by the horns and find ways to improve the situation. My determination paid off: In recent years I've found several strategies that have increased patient flow through our office, dramatically reducing patient wait times. I've also changed the way I interact with frustrated patients, mitigating their anger if wait times do end up being longer than they'd like.

I believe that implementing these strategies has left me with much happier patients and less stress for me and my staff. Here, I'd like to share some of what I've learned, so that you can consider implementing some of these changes in your own practice.

Three Patient Flow Boosters

My first goal was to reduce the time our patients spent waiting in the office. I've implemented several strategies that have helped to accomplish this. These include:

• ***When possible, see patients in the order they arrived.*** Our electronic health records system allows us to look at our patient schedule in the order that patients checked in (as opposed to when they were scheduled to be seen). *(See example, facing page.)* If your system allows you to see that, you can make sure that the patient who got there the earliest is the one you see next. Although this might sound unfair, it ensures that no patient waits a long time simply because they arrived early.

Of course, it doesn't always make sense to do this; if a patient checked in a lot earlier than their appointment, it's not really fair to see them first. However, if you do, they walk out very happy. That can give a nice boost to your day. So I try to see patients in "checked in" order.

• ***Keep the patient in one room while the doctor moves from room to room.*** A common arrangement in many practices is that the MD sees patients out of one or two rooms, each with a scribe. In addition, there are two or three other rooms in which patients are being worked up by technicians. That means that the work flow is: 1) The patient checks in and goes to the waiting room; 2) the patient is called into a room by a technician and is worked up; 3) the patient goes back to the waiting room; 4) the patient is called into the physician's room and seen by the physician; and 5) the patient leaves.

To eliminate the repeat visit to the waiting room, we keep the patient in a single room once the visit is underway; instead of the patient moving, the doctor comes in and leaves. So in our system, the patient checks in and goes to the waiting room; then they get called into an exam room by a technician who works them up. Then, instead of sending the patient back to the waiting room, they stay in that room, and the doctor is notified to go to that room to see the patient. In many cases, the technician who's been working up the patient becomes the scribe during the doctor's visit. When that's complete, the patient leaves the practice.

With this system, I'm not just working out of one or two rooms that are "mine," I'm working out of all of my rooms. I'm hopping from room to room—whichever room the team tells me is where my next patient is.

Note: A key factor that allows this to work is that I cross-train as many of my technicians and scribes as possible to be able to do both tasks. This may be easier said than done, but if you can do that, even with one or two of your team members, it can be really helpful. If cross-training your techs to be scribes isn't possible, then one of your scribes can follow you from room to room, or you

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

can simply see occasional patients without a scribe.

• ***Use desktop group-chat software to keep all team members apprised of patients' location and status.*** Every technician and physician is usually in front of a computer during the workday. Our computers run Microsoft Office, and one of the pieces of software built into that suite is Microsoft Teams, which allows the members of a "team" to communicate between work stations. One of my techs suggested that we could chat with each other using this, making it possible to coordinate our movement between rooms. It turned out to be great for that purpose.

What this means is that every morning when our technicians log onto a computer, we create a "team" that allows us to chat onscreen. When MS Teams is running in the background, if someone in the team sends a message, it shows up in the lower right hand corner of the screen. For example, a note directed to me might say "Room 12 next." That tells me where to go after I'm done with the current patient. Or, it might show a question a technician has about a patient, or give an instruction from a scribe to one of the techs, such as "get Mr. Johnson into your room next."

This has turned out to be a very useful tool that we weren't previously using. It allows us to avoid having to get out of our chair, go to the other room, try to figure out what's happening and determine who needs to be where. In short, it eliminates a lot of wasted effort.

Practical Results

It's hard to quantify how much this altered workflow has shortened waiting times overall, but it's clear that patients are getting in and out more quickly and are less upset about extended waiting times. For example, let's say I have a patient coming in for an eye pressure check and a visual field test; we're not dilating the patient that day. In the old system, they might show up at 1:00 p.m. for the visual field test; they'd be worked up by the technician and be done by 1:45. Then they'd go back to the waiting room. I might still be seeing my 12:00 or 12:30 appointment, so they wouldn't get into my room until 2:15 or 2:30. I'd spend about two minutes with them going over their test results, and then they'd leave.

Checked In	Dilated	Department	Time
7:17 AM		MGCOCBBOSGL	7:30 AM
7:20 AM		MGCOCBBOSGL	8:00 AM
7:22 AM		MGCOCBBOSGL	7:30 AM
7:24 AM		MGCOCBBOSGL	7:30 AM
7:37 AM		MGCOCBBOSGL	8:15 AM
7:41 AM		MGCOCBBOSGL	7:45 AM
7:43 AM		MGCOCBBOSGL	8:45 AM
8:19 AM		MGCOCBBOSGL	8:30 AM
8:28 AM		MGCOCBBOSGL	8:45 AM
8:34 AM		MGCOCBBOSGL	9:00 AM
8:49 AM		MGCOCBBOSGL	9:15 AM
8:56 AM		MGCOCBBOSGL	9:45 AM
9:17 AM		MGCOCBBOSGL	9:45 AM
9:26 AM		MGCOCBBOSGL	9:30 AM
9:26 AM		MGCOCBBOSGL	10:00 AM
9:52 AM		MGCOCBBOSGL	10:00 AM
9:56 AM		MGCOCBBOSGL	10:30 AM
10:06 AM		MGCOCBBOSGL	10:30 AM
10:08 AM		MGCOCBBOSGL	10:15 AM
10:11 AM		MGCOCBBOSGL	10:30 AM
10:32 AM		MGCOCBBOSGL	11:00 AM
10:32 AM		MGCOCBBOSGL	10:45 AM
10:47 AM		MGCOCBBOSGL	11:00 AM
10:50 AM		MGCOCBBOSGL	10:45 AM
11:10 AM		MGCOCBBOSGL	11:15 AM

One way to keep patients happier and keep flow moving through the office is to see patients in the order they arrived, rather than at their pre-made appointment time. (It helps if your EHR can list patients in this order, as shown above.)

In our new system, they'll check in at 1:00 for the visual field test and be done with that test by 1:30. Their appointment with me is at 1:30, so they get called in by a technician at 1:30 or 1:40. They get worked up and have their eye pressure checked by the technician, who then calls me in. I might double-check the pressure and then go over the visual field results. So, the patient arrives at 1:00, and has left the practice by 2:00. Essentially, their appointment lasts about 30 minutes less than before, and instead of sitting in the waiting room feeling like they're being neglected, the extra time before I see them is usually spent talking to the technician in the exam room until I come in.

Admittedly, this system isn't perfect. In the old system, the technician could grab the next patient to work up after taking the current one back to the waiting room. In my new system, the technician's room isn't available for the next patient because there's someone in there waiting for me. But because I'm running between four or five rooms, patients don't actually wait very long.

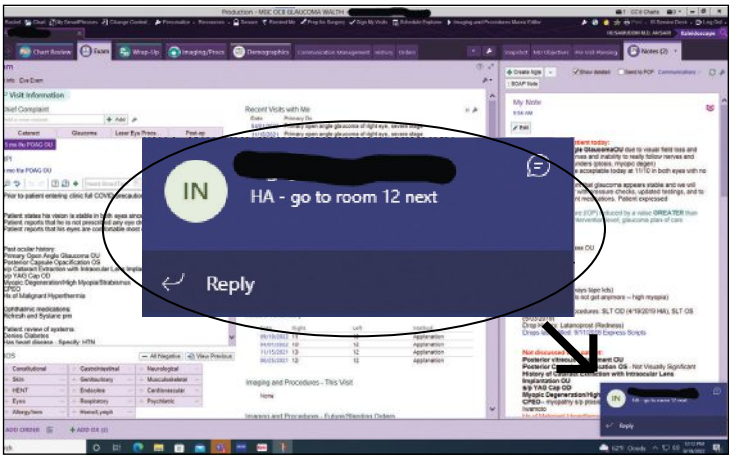
Another advantage of our new system is that patients coming in for one simple reason, such as an eye pressure check, can get in and out quickly. In a sense, it gives them a way to "jump the line." The technicians identify these patients and make sure they get finished up quickly, without disrupting the flow for other patients who need more time and attention.

Another advantage is that in the old system, the patient encounter didn't end until the patient left my room. Then, I'd have to wait for the scribe to bring in the next patient. With the new system, the patient encounter is ended by me; I get up and move to the next room in which I'm needed. This avoids bottlenecks and wasted time. (Of course, this doesn't mean that I'm cutting off the patient so that I can leave the room. It just means when I ask "Any other questions?" and they say no, I say, "Go ahead to the front desk and check out, we'll get you out of here," and then I leave.)

Smart Telemedicine

Another way we've gotten our patient flow under better control and reduced patient cycle time is by implementing telemedicine in a nonstandard way. Patients often have questions that can require fairly extensive answers. For example, we do a lot of cataract surgery. Patients sometimes leave their cataract evalu-

ation visit without having decided on what type of IOL they want. Or, a patient may ask a complex question such as "Am I going blind?" In that situation I may say, "No, if you stick with our plan of taking your medications and following up when I ask you to, the likelihood of you ever being impaired because of glaucoma is miniscule." That's enough for some patients, but if it's not, a longer discussion is called for.



Some software programs allow anyone in the office to send messages that appear in the lower corner of the screen on computers in other rooms. This is useful if the doctor is moving from room to room to see patients instead of staying in one room with patients being brought to him or her.

The problem is that having an extensive discussion with a patient during a busy clinic day can be very stressful, and it adds to cycle times, especially if the patient is in a really challenged state and needs time to think, process and ask questions. Ideally, those questions should be answered when it won't hold up patient flow.

One solution would be to talk to the patient over the phone outside of business hours. However, I've always found this unappealing. I don't want to give up personal time; I don't want to play "phone tag" with multiple patients; and I never felt comfortable billing for the time involved. For those reasons, I never considered using the phone as a tool to reduce cycle time. I felt that anything I needed to discuss with a patient should be discussed while the patient and I were face-to-face, even if it slowed down our patient throughput.

Today, I've found a way to use telemedicine that avoids the downsides I was concerned about. Instead of saying "Let's talk on the phone after hours today or tomorrow," I have the patient schedule a call with our receptionist at a specific time during one of our clinic days, in a window set aside expressly for the purpose of having longer conversations with patients.

Offering this option to patients (when needed) is greatly appreciated by the patients. Actually, many patients don't even take me up on the offer; they realize they're all set, they don't need any more time, and they just end the visit. But if I make that offer to four patients a day and they do take me up on it, four 15-minute conversations that would have slowed down patient flow and increased waiting times are now moved to a time slot reserved for that purpose that won't interfere with patient throughput. That benefits both myself and all of our patients.

If a patient wants to schedule a call, my secretary puts them on my clinic schedule at a later date. In the schedule she notes the name of the patient, time of the appointment, phone number of the patient and the general topic we'll be talking about. It may be on my schedule at 4:30, but the patient only knows that they'll get a call from me between 4:00 and 6:00. They're instructed to be available during that time period, and it's very rare that they don't answer.

From my perspective the benefits of this system are multiple: The calls are listed on my clinic schedule, so I never forget one; I almost never have to play phone tag; the calls rarely eat into my personal time; I don't forget to document the phone call, because it's a clinic encounter that'll remain open until I close it by documenting what we talked about; I can often do it during my drive home; and patients really appreciate it. The bottom line is that I don't make random phone calls to patients anymore.

Making Telemedicine Work

Other things about this telemedicine system worth mentioning include:

- ***You can use it to reply to patients who call in with questions.*** I don't limit this tool to patients who need a lot of time in clinic; I also use this tool for any patient who calls with a question—about anything. For example, I may get a message saying, "I'm having a side effect from this eye drop. What should I do?" It's a time and energy sink to try calling them back at random, with no idea if they'll answer, or to ask my secretary to leave a voicemail with my instructions. (I can't be sure my instructions will reach the patient accurately.) I used to let messages pile up in my in-basket because I was too tired to call patients back, and I never knew what to do if they didn't answer. This system eliminates all of that; I simply tell my secretary to schedule the patient for a telehealth call in the next couple of weeks.
- ***Some of these phone conversations may be billable.*** Whether this is true may depend on factors such as how close the call is to the initiating visit. But to be honest, I don't care that much about the billing. If I collect a little income, that's great. But even without that, just based on the time savings, it feels like a win. Furthermore, I get to provide good care for these patients without feeling pressured by the knowledge that

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1. Market Scope 2021 Ocular Surface Disease Survey
2. Lemp, MA., et al. Cornea. 2012;31(5),472-478.

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other patients are waiting to see me. And my patients really appreciate it.

• ***You can invoke the pandemic to shorten the in-office conversation.*** To get a patient to save questions for the phone call, I often invoke the pandemic. I'll say, "I've got all the data I need now, and I want to answer all your questions and help you decide what to do next, but we can't do that right this minute. As you know, we can't have patients hanging around the office because of the pandemic. I'd like to get you out of here and not let the waiting room get too full. Let's schedule a phone call to discuss my recommendations."

Getty Images

When patients are upset, a key strategy for preventing a wider crisis in the office is to accept the blame and be caring and warm toward the patient—even if that's the last thing you feel like doing.

Being able to invoke the pandemic and not apologizing for it is important. I just say, "You remember, Mr. Jones, how long you used to have to wait in our office? Well, we're not doing that anymore." Most people are onboard, especially if you offer the fallback option of the phone call. (I don't think I could be as abrupt with them in the office if I wasn't able to offer a phone call to give them more of my time.) The majority of patients don't take me up on the phone call offer, but it helps them understand that the appointment is ending, and I'm available if they need further consultation.

Of course, it's reasonable to wonder whether this is burdensome for the doctor. I certainly haven't found it to be; it's actually been a lifesaver. I recently looked back at a six-month period; out of 4,000 patient encounters, 50 were telemedicine, which isn't even one per day. Generally, I make one to three calls per week.

Managing Upset Patients

Of course, no matter how much you're able to improve patient flow in your practice, you'll inevitably encounter a patient who's upset about the length of the wait. Most of us are working very hard to provide excellent care and probably feel stressed when patients are backlogged. So it's tempting to react angrily when a patient expresses unhappiness about a long wait. As you'd expect, doing that will backfire. If you inflame the situation with your own anger, it can get very ugly very quickly.

Using the following strategies will help maintain peace in your clinic and keep an upset patient from becoming even more upset:

• ***Take the high road.*** Instead of venting, take a deep breath and suppress your own feelings. Accept the blame for the wait and display an attitude of caring and warmth; tell the patient that you're working to make the situation better. This may not be what you're actually thinking, but it will calm the patient down and help keep them from developing a negative opinion of your practice. The idea is to manage the situation in the way that's most likely to get the result you want, rather than simply venting your true feelings (as good as that might feel).

My practice manager frequently speaks with upset patients; her mantra is "Kill them with kindness." It really works. Of course, it doesn't always feel good, because when you're at your wit's end you really want to lash out. But again, it gets the result you want.

• ***Have specific phrases you can use, so you don't have to improvise.*** Things you can say in this situation include:

— "I'm sorry for the long wait. We have to do better." In many cases, this one statement is enough.

— "I know you've been waiting a long time. I know it feels like we don't respect your time. I'm sorry, but I promise I'm here for you 100 percent now." This defuses the situation and encourages the patient to focus on the fact that the wait is over and you're giving him or her your full attention.

— "We're going to keep working on ways to reduce our wait time. But in the future, please do expect to be here for X number of minutes" (whatever number you think is reasonable or realistic). Once you've supported the patient by accepting responsibility, you can set more realistic expectations for future visits.

• ***Explain the need to see unexpected emergency patients.*** Sometimes it helps to offer an explanation for the long wait. I'll sometimes go out to the waiting room and say, "I'm so sorry, we've had several emergencies today and we're working very hard to see everyone. We really appreciate your patience." Usually, the statement that we've had several emergencies is true; it's a frequent occurrence. (Once or twice I've said this to mitigate a particularly tough situation when it wasn't entirely true.)

Of course, you may find that patients who've been waiting wonder why seeing emergency patients is even an issue. If I believe that the patient asking about this might be receptive to understanding the situation, I'll explain that when someone has a crisis involving their eyes, they can't go to the hospital emergency room; they have to come to us. A hospital ER isn't equipped to man-

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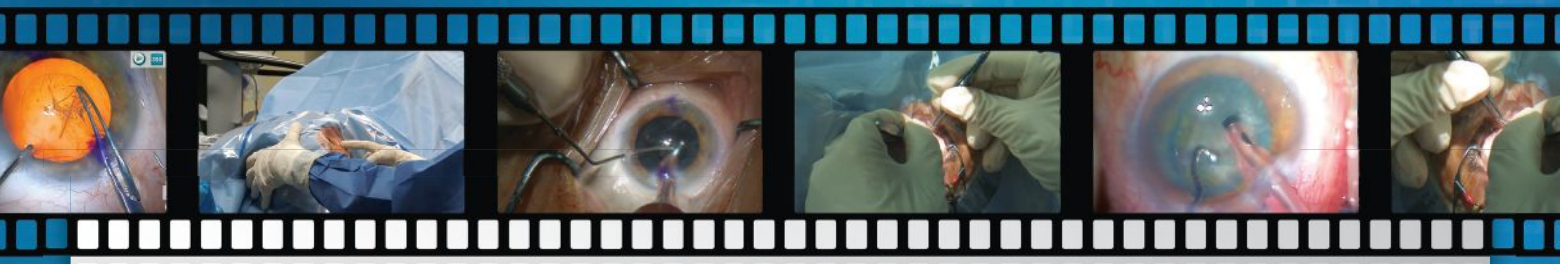

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age an ocular emergency. The reality is, if a patient goes to the ER with an eye problem, they're most likely going to walk out with an antibiotic drop and a follow-up appointment later that afternoon at the ophthalmologist's office. So unexpected additions to our schedule are unavoidable—and those patients can't be postponed. The result is that some of the patients who were previously scheduled will have to wait longer.

Patients sometimes ask why we don't just reserve some slots for those patients. I explain that unfortunately, the volume of emergency patients is significant. In fact, those slots get booked up as soon as you make them, so when another emergency patient comes in, they need a slot that doesn't exist. That means that the patients who are scheduled have to wait. (To be honest, we haven't come up with a way to avoid this problem, so we often have to tell our patients that this is just the way it is. Our office is a de facto "eye emergency room," every day.)

I do find that explaining this, when appropriate, really does help patients understand what we're up against. Every eye doctor is in the same position, and we can't just work around the clock. We do have to go home to our families at some point.

Generally, when I explain this, patients are receptive and understanding.

The Challenge of Change

I realize that some of these changes wouldn't be easy for every practice to make. Many doctors work in large health systems and don't have the authority to say that they want to start including telehealth slots in their clinic schedule, or that they want to start cross-training their techs and scribes. On the other hand, I suspect that small practices, where doctors have a lot of autonomy, might be able to implement many of these ideas.

Even I have encountered some bumps in the road in that regard. Most of my practice partners work out of a single exam lane, so I sometimes wonder if my patients think I'm too rushed when they see me hopping back and forth between exam lanes. But if they do, that's minor. The overall result has been shorter waiting times for my patients and reduced stress for me.

ABOUT THE AUTHOR

Dr. Ansari is a glaucoma specialist and co-director of the glaucoma fellowship at Ophthalmic Consultants of Boston. He receives research support from Alcon, AbbVie/Allergan, New World Medical and Nicox, and is a consultant for New World Medical.

(Continued from p. 68)

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(Continued from p. 47)

Dry-Eye Diagosis: Pearls for Success

test, the MMP-9 can also be useful in evaluating treatment response.

• ***Schirmer's test.*** Among the oldest objective tests for measuring dry eye, the Schirmer's test is still used today by many clinicians to assess tear production. "Especially for new patients referred for dry eye, I'll conduct a Schirmer's test, but I'll do it with anesthesia so I can find out what the basal tear secretion is, not the reflex tearing," says Dr. Rapuano. "If the score is greater than 10, or certainly greater than 15, aqueous deficiency is lower on my list of potential causes. If the score is five or below, aqueous deficiency is much higher on my list. If they score in the gray area between five and 10, the Schirmer's test may not be super helpful," he explains. "This is not the greatest test in the world, and it has a lot of variability, but it can help confirm patients with very low or normal tear production."

Dr. Akpek, on the other hand, chooses not to use anesthesia when conducting the Schirmer's test. "Unanesthetized Schirmer's, but not anesthetized Schirmer's, is included as a criterion in the classification criteria for Sjögren's syndrome," she explains. "In evaluating a patient with any ocular surface disease, I want to make sure there are no underlying systemic diseases (i.e., Sjögren's, sarcoidosis, scleroderma or graft versus host disease) because those patients are managed, examined and treated in a different way." Dr. Akpek adds that the most common underlying conditions for any ocular surface disease are thyroid eye disease and Sjögren's. "If the Schirmer's score is five or less, I definitely consider the possibility of Sjögren's in that patient," she notes.

Takeaways

There are numerous possibilities of what could be causing your patient's dry eye, but there are also dozens of tests and tools that can help you reach the right diagnosis. "Despite dry-eye testing being available, it's not taken advantage of by providers," says Dr. Akpek. "Any patient coming in for an exam should be evaluated for signs or symptoms of dry eye, and if they have either, review the history, perform a battery of tests and then go from there." ◀

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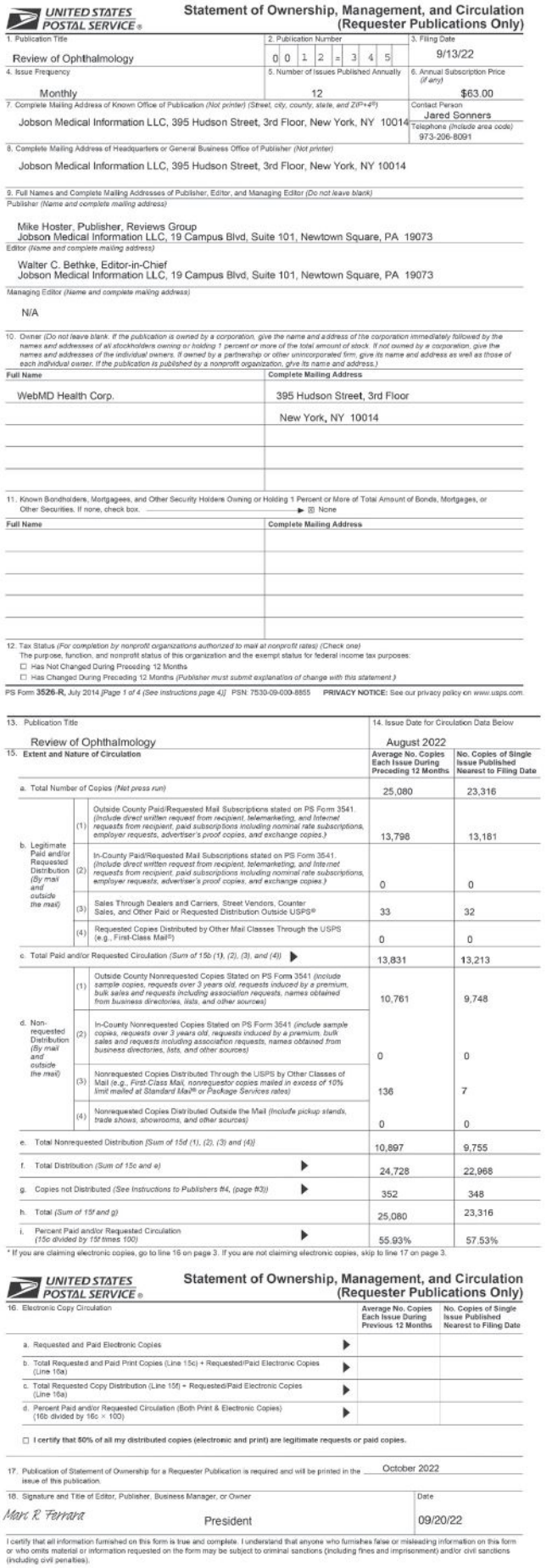

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WILLS EYE RESIDENT CASE REPORT

A 78-year-old woman presents with retinal vascular sheathing and floaters.

HANNAH GARRIGAN, MD, AND JAMES P. DUNN, MD
PHILADELPHIA

Presentation

A 78-year-old Caucasian female was referred to uveitis clinic for further evaluation of perivascular sheathing and floaters in the right eye. She had a history of ocular toxoplasmosis in the left eye, confirmed by PCR of an aqueous sample, for which she received intravitreal clindamycin 10 years prior. Her visual acuity was chronically count-fingers in the left eye due to peripapillary and papillomacular involvement *(Figure 1)*. Due to her monocular status, she was debilitated by her new-onset floaters in the right eye. She endorsed no pain or photophobia.

Medical History

Her complex medical history included active chronic lymphocytic leukemia (CLL), diverticulitis status post-colonic resection, hepatitis B, congestive heart failure and hypertension. Her medications included venetoclax (BCL-2 inhibitor), tenofovir, entecavir, carvedilol, lisinopril, prophylactic acyclovir, fenofibrate, cyclobenzaprine, omeprazole, lorazepam, gabapentin and duloxetine. Ocular history included bilateral cataract surgery several years prior and toxoplasmosis of the left eye as described above. She had no relevant family history. She denied cigarette smoking or drug use, and she drank one to two alcoholic beverages a week.

Examination

On initial presentation, visual acuity was 20/20 OD and CF OS. Pupils were equally round and reactive with no afferent pupillary defect. Intraocular pressure was 14 mmHg OD and 11 mmHg OS. The anterior exam was normal in both eyes, with no keratic precipitates, cell, flare or iris transillumination defects. Both PCIOLs were well-positioned in the capsular bag. The posterior exam was significant for 1+ vitreous cell and moderate vitreous debris OD, with no evidence of vasculitis and no lesions besides a choroidal nevus present in the periphery. The left eye had trace vitreous cells and an inactive chorioretinal scar sparing the fovea as seen in Figure 1.

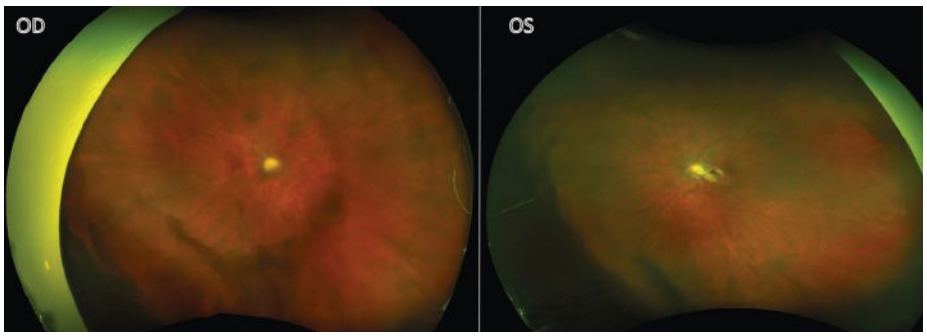

Figure 1. Bilateral fundus photos taken at initial visit.

What's your diagnosis? What further work-up would you pursue? The diagnosis appears on p. 81.

Work-up, Diagnosis and Treatment

At initial presentation, the differential included infectious (syphilis, Lyme, toxoplasmosis), inflammatory (sarcoidosis), neoplastic (lymphoma) or iatrogenic (biologic use) etiologies. It was suspected that the patient's chemotherapy agent, venetoclax, might be associated with the ocular inflammation. Sub-Tenon's triamcinolone 20 mg/0.5 mL was administered superotemporally OD.

One month later, the patient returned for follow-up and was found to have an area of inferonasal retinal whitening in the right eye *(Figure 2)*. The peripheral lesion was fluffy white with creamy edges and severe vitritis. Visual acuity remained stable at 20/25+1 OD, although she complained of subjectively worsening vision. Fundus autofluorescence imaging showed hyperautofluorescence of the lesion OD, in contrast to the hypoautofluorescent scar in the left eye. Lab testing was pursued, with CBC only notable for mild thrombocytopenia (platelet count 134K) and CMP within normal limits. Serum ACE, Lyme, RPR, interferon gamma releasing assay (QuantiFERON Gold Plus) and *Toxoplasma gondii* IgG and IgM testing were negative. Given the inconclusive blood work, the decision was made to perform an anterior-chamber tap for PCR testing, which was negative for HSV-1/2, CMV and VZV, but positive for *T. gondii* (3,300 copies/mL). She was treated with sulfamethoxazole-trimethoprim (TMP-SMX) twice daily and intravitreal clindamycin 1 mg. She didn't tolerate TMP-SMX, and thus was switched to azithromycin 250 mg/day.

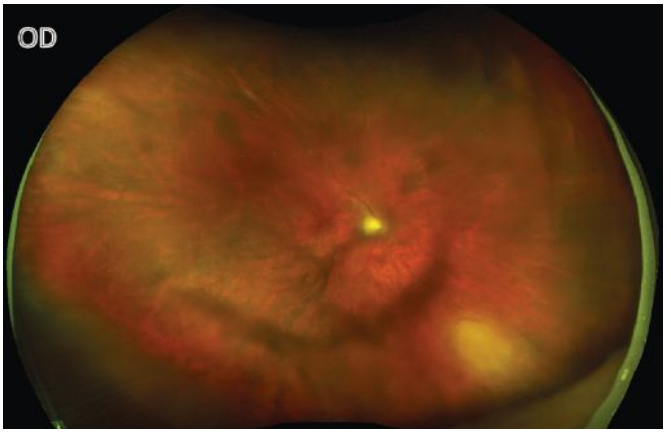

Figure 2. The right fundus a month after sub-Tenon's triamcinolone injection with new active lesion present inferonasally.

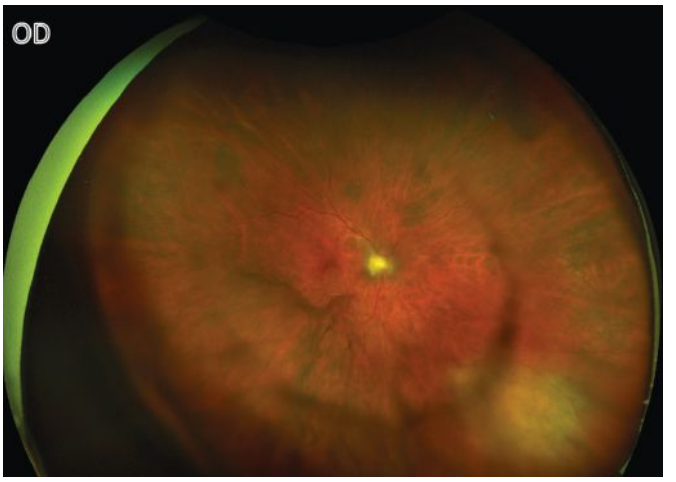

Figure 3. A right-eye fundus photo two months after initial visit with improving inferonasal toxoplasma lesion.

She returned a week later with persistent blurred vision and floaters but stable acuity. She was treated with prednisone 30 mg daily with a weekly taper. A month later, the lesion showed less active borders *(Figure 3)*. This patient continued to be closely followed.

Discussion

In this case, a 78-year-old immunocompromised woman with prior ocular toxoplasmosis OS presented with new intermediate uveitis OD. She was treated with a sub-Tenon's triamcinolone injection resulting in an acute worsening of symptoms and a new peripheral retinochoroidal lesion. This is an unusual case of ocular toxoplasmosis, given the initial presentation of intermediate uveitis, bilateral toxoplasmic involvement in a non-endemic region, and negative IgG and IgM serological testing with *T. gondii* DNA detected in the aqueous humor.

Typically, acute ocular toxoplasmosis presents as unilateral retinochoroiditis with the classic "headlight in the fog" appearance with fluffy white edges and haze due to vitritis.[1] As seen in Figure 1, this patient's ocular toxoplasmosis initially presented with vitritis but no visible lesion. Cases have been reported of infected individuals with transient episodes of intraocular inflammation, but the pathophysiology is unknown.[1] Other signs of this protozoal infection can be anterior uveitis (granulomatous or non-granulomatous), satellite lesions, vasculitis and inflammatory ocular hypertension; our patient didn't have any of these findings, however. Given the clinical picture with no visible retinitis, an inflammatory or iatrogenic etiology was higher on the differential and periocular steroids were administered to preserve vision in a monocular patient. Even in immunocompetent patients, periocular steroid injections given for toxoplasmosis can lead to fulminant eye disease, particularly in those who haven't received anti-parasitic therapy.[2] In this patient, the

sub-Tenon's triamcinolone injection likely catalyzed the onset of the retinochoroiditis.

TMP-SMX or other antibiotic therapy may be used to control the parasites' reproduction in the active phase while the patient is on topical and systemic steroids. Unfortunately, toxoplasmosis is incurable, as the bradyzoite form residing in tissue cysts doesn't respond to antimicrobials. In most immunocompetent patients this infection is self-limited.[3]

Given the epidemiology of ocular toxoplasmosis, bilateral disease and reinfections are atypical in the United States. Although the seroprevalence ranges from 22.5 to 80 percent, increasing with age, the prevalence of infected individuals with ocular manifestations is estimated to be around 2 percent.[4] In contrast, 17.7 percent of those infected in Brazil have evidence of toxoplasmosis affecting the retina. France similarly has a high prevalence of *T. gondii* infections with 67 percent of pregnant women being IgG positive.[4] There are theories about what may cause the recurrence of toxoplasmosis, including trauma and hormonal changes, but immunosuppression is not thought to be a trigger.[5,6] Our patient didn't recall any inciting incident. Bilateral involvement is more likely in congenital toxoplasmosis infections versus acquired, but it isn't considered a distinguishing factor in the diagnosis.[7]

This case brings to focus important differences in interpreting diagnostic testing for ocular toxoplasmosis for those who are immunocompromised compared with those who are immunocompetent. In an immunocompetent individual, a non-reactive IgG and IgM essentially rule out toxoplasmosis infections. A study in Brazil determined that a negative IgG serology has a 91-percent negative predictive value.[8] In contrast, a positive IgG and IgM serum test indicates past or recently acquired infection, respectively, but doesn't localize the infection to the eye.[9] Our patient had CLL and was undergoing treatment with a BCL-2 inhibitor, both of which impair her ability to produce antibodies during infections.[10,11] Therefore, she didn't produce detectable immunological memory to the *T. gondii* infection in her left eye 10 years prior, which increased her likelihood of multifocal disease and reinfections. Given this patient's atypical presentation and threat to her only functional eye, it was clinically justified to proceed with the more invasive anterior chamber paracentesis to ensure she was being treated appropriately.

PCR testing in ocular toxoplasmosis has lower sensitivity (36 to 55 percent) than in acute retinal necrosis (roughly 90 percent) and may vary according to the strain of the Toxoplasma organism.[12] On the other hand, PCR testing has a 100-percent positive predictive value in ocular toxoplasmosis.[13] Thus, a positive PCR test is diagnostic, but a negative PCR test doesn't definitively rule out the disease. The use of other diagnostic tests, such as the Goldman-Witmer coefficient and immunoblotting, may reduce the risk of false-negative results;[13] however, these aren't commonly used in the United States.

Other investigators have suggested that combining PCR testing from both the aqueous and vitreous humor may increase the diagnostic yield in atypical cases of ocular toxoplasmosis in immunocompetent patients, in whom the yield from aqueous humor specimens may be substantially less than in immunosuppressed patients.[12,14] The low DNA detection rates in immunocompetent patients suggest that there is a low parasitic burden in the aqueous and that the onset of symptoms and inflammation could be driven by a robust immune response rather than the activity of the parasite.[14] Due to the detectable PCR load (3,300 copies/mL) and classic retinochoroidal lesion after steroid administration, our patient didn't require further testing.

In conclusion, ophthalmologists should have a high clinical suspicion of atypical presentations of toxoplasmosis in those who are immunocompromised, as the disease could take on an aggressive course. When in doubt about the diagnosis with a potentially vision-threatening disease process, it is important to obtain aqueous testing, as serum IgG and IgM may not be sufficient in those who are immunocompromised. ◀

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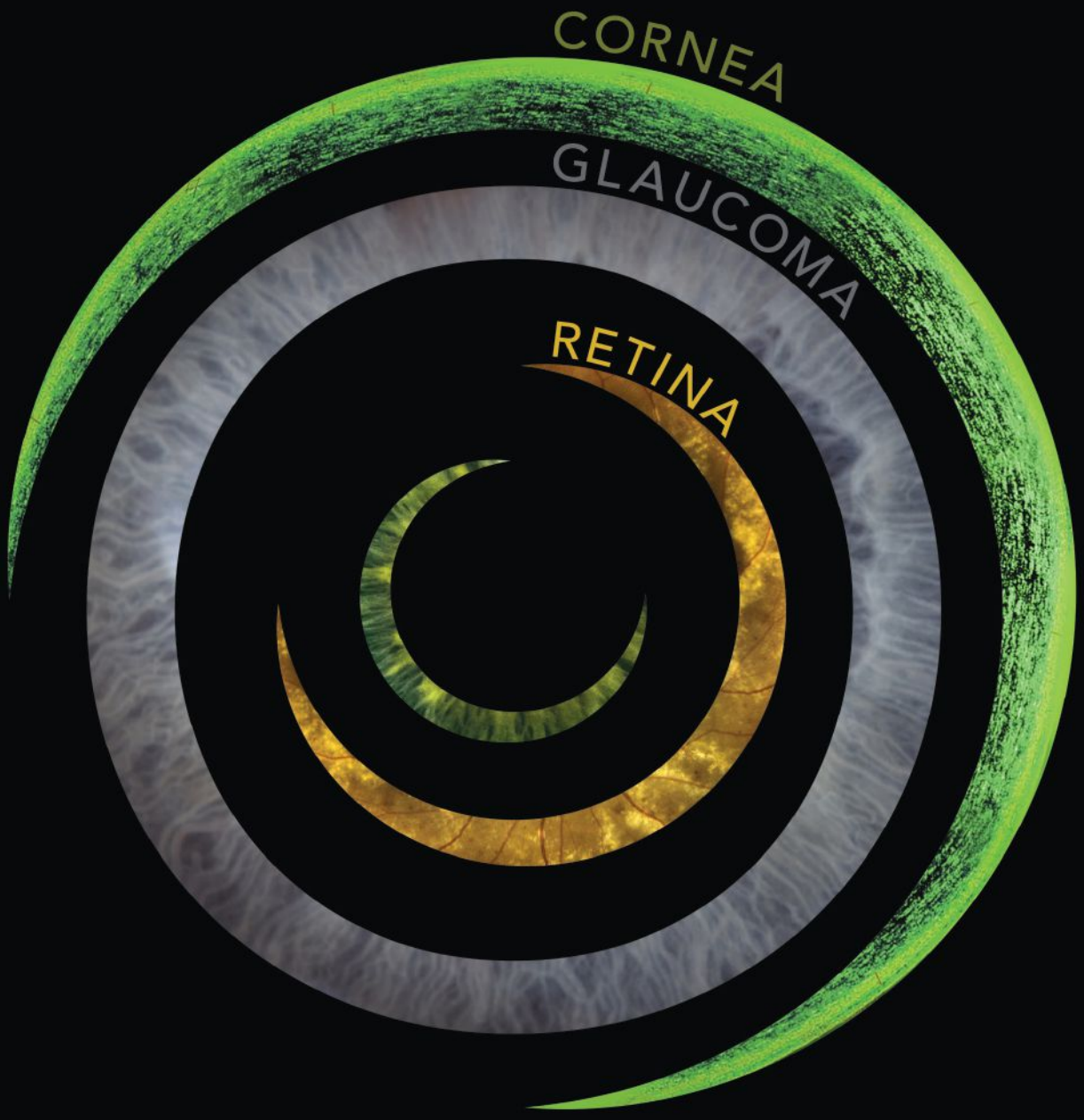

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