Wills Eye Resident Series: A 47-year-old Man Presents with Fullness in his Left Eye, *p .94*

REVIEW® of OPHTHALMOLOGY

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DEFYING ECONOMIC GRAVITY: 10 WAYS TO BOOST INCOME

Doctors share ideas that have helped keep their balance sheets out of the red. **P. 30**

ALSO INSIDE:

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

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

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

Indication

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

Important Safety Information

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

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KEN JEONG,
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Dry eyes deserve a change

Important Safety Information (cont)

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

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

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

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

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

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

6.2 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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NEWS

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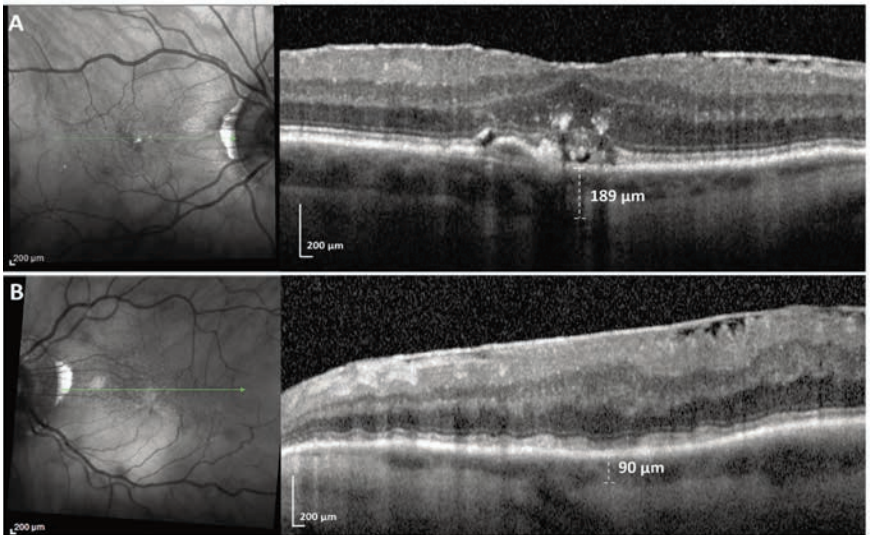
NOVEMBER 2021

Retinal Deposits Linked to Cardiovascular Disease

Researchers in New York City believe they may have found the link tying together age-related macular degeneration—today's leading cause of blindness—and cardiovascular disease—today's leading cause of death. The MDs behind this development explain that the link has been elusive because both AMD and CVD are "umbrella" categories, and the link only becomes apparent when looking at the right subgroups.

"There are two fundamental forms of early macular degeneration, and they're very different," notes R. Theodore Smith, MD, PhD, a professor of ophthalmology and neuroscience at the Icahn School of medicine at Mt. Sinai in New York City, and the director of biomedical imaging at the NY Eye and Ear Infirmary. (His partner in developing this theory is K. Bailey Freund, MD, a clinical professor in the Department of Ophthalmology at NYU Grossman School of Medicine.) "One causes drusen; the other causes what are called subretinal drusenoid deposits," Dr. Smith says. "Both can progress to 'wet' macular degeneration, but the drusen are the result of a local process, not hardening of the arteries. Only the subretinal drusenoid deposits are triggered by poor vascular perfusion."

Dr. Smith notes that surgeons can miss the subretinal deposits on OCT because they tend to be more peripheral, out toward the arcades, especially superiorly. "That's because of gravity," he says. "When blood flow becomes insufficient, the superior vessels lose flow first; over time, the deposits appear lower and lower. In contrast, drusen, driven by local factors, tend to start in the central retina. The location difference may also relate to rods and cones; drusen tend to appear among cones, which are largely in the middle of the eye; subretinal deposits tend to appear amidst rods, which are more peripheral."



A patient who has had a stroke on the left side. The top scans show the unaffected right eye; the visible lumps are soft drusen, lying underneath the RPE. The left retina (bottom scans) is packed with subretinal deposits on top of the RPE, caused by poor perfusion following the stroke. On the right, they create a wavy appearance in the layer above. The *en face* scan on the left has small, dark dots widely spread, with more toward the top of the image; those are the subretinal deposits. Note that the choroid layer has shrunk from 189 µm in the right eye to 90 µm in the left eye, a consequence of insufficient blood flow.

So what's the clinical value of catching these in a scan? "In terms of caring for the eyes, you wouldn't do anything differently than if you found drusen," says Dr. Smith. "If there's no neovascularization, you follow the patient and see what happens. However, those deposits won't form unless there's inadequate blood flow to the retina, which almost certainly means there's inadequate flow systemically. So, if I find those subretinal deposits, I send the patient to a cardiologist or neurologist. This patient may be in serious danger of having a stroke or heart attack."

Dr. Smith says surgeons don't usually look at the superior part of

(Continued on p. 8)

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Retinal Deposits

(Continued from p. 5)

the scan. "They're looking at the central macula for the fluid buildup from choroidal neovascularization," he says. "The first place I look when I'm reviewing an OCT scan of a macular degeneration patient is the superior macula. If the deposits are up there, I'll spot them. If I don't find them there, I probably won't find them anywhere else."

Dr. Smith points out that the other way to find subretinal deposits is to look at the *en face* image of the retina on the left-hand side of the OCT scan. "On those scans drusen look like bright or reflective spots. There will be more in the middle, and they're different sizes. The subretinal deposits are a bunch of little dark dots, all the same size, and spread around uniformly. People tend to ignore them because they don't know what they are. They may also escape notice because the left-hand image often shows 30 green scan lines at once, making it a challenge to evaluate the underlying image. But with one click you can turn off the grid pattern and just see the picture. Then it's much easier to spot those little dark dots."

RRD Repair: Is Slow and Steady Best?

Single-operation success has long been held as a marker for surgical success, but a new post hoc analysis of the PIVOT trial data presented at the Retina Society and ASRS this year suggests that even though pneumatic retinopexy has a lower single-operation reattachment rate than pars plana vitrectomy, it seems to induce fewer anatomic abnormalities that affect long-term visual acuity.

"We've been learning over the last few years that it's not just about how often but how well you reattach the retina," says Rajeev Muni, MD, FRCSC, an assistant professor in the department of ophthalmology and vision sciences at the University of Toronto.

One of these abnormalities is outer retinal folds, which are partial-thickness folds of the photoreceptor layer. "Instead of the photoreceptor layer being in contact with the RPE, it's folded in such a way that the photoreceptors are in contact with each other," Dr. Muni says. He and his group assessed the incidence of postoperative ORFs in PPV and PnR following rhegmatogenous retinal detachment.[1]

"We assessed the macula-off patients from the PIVOT trial and found that there were differences in their functional outcomes based on whether they had folds or not," says Wei Wei Lee, MD, a retina fellow at the University of Toronto. "In the PnR group, the risk of ORFs was 14.3 percent, and in the PPV group, the risk was significantly higher at 34.1 percent (p=0.011)."

An en face OCT image of a patient's retinal folds.

Dr. Lee says all folds resolved before six months, except in one PPV case which took eight months. "When we compared all PnR and PPV patients who had folds at one month and those who didn't, there was a 9.4-letter difference in ETDRS visual acuity—almost two lines of vision, with vision being worse in patients with early ORFs. Mean ETDRS acuity was 65.7 in patients who had ORFs at one month and 75.1 in patients who didn't have ORFs at one month."

Dr. Muni says there's a possibility that something else about PnR or PPV is causing these differences in vision. "Perhaps ORFs are correlative but not causative," he says. To learn more, the team performed a subgroup analysis of the PPV patients. "There was a 12.6-letter difference between those who had outer retinal folds (62.8 letters) and those who didn't (75.4 letters). This was powerful data. It tells us that this anatomic outcome that we can detect on imaging has a significant impact on long-term visual acuity. We also found that the closer the folds were to the fovea, the stronger the correlation with vertical metamorphopsia.

"Even though the PPV single-operation reattachment rate is greater by 12 percent, is it worth it if patients have these microstructural or other anatomical abnormalities and have worse vision?" adds Dr. Muni, who prefers first-line PnR. "A patient's final vision matters most to me."

He proposes a modified vitrectomy approach to avoid ORFs, called minimal-gas vitrectomy. "We perform a full vitrectomy but then put just a small gas bubble in and leave the retina to reattach itself naturally by the RPE pump," he says. "A detached retina causes little corrugations. In another study we recently published, we found the retina reattaches in five specific stages.[2] We learned that the corrugations resolve in stage two, before the retina comes in contact with the RPE, which is stage three. By draining fluid in vitrectomy, you're basically rushing through stage two

(Continued on p. 16)

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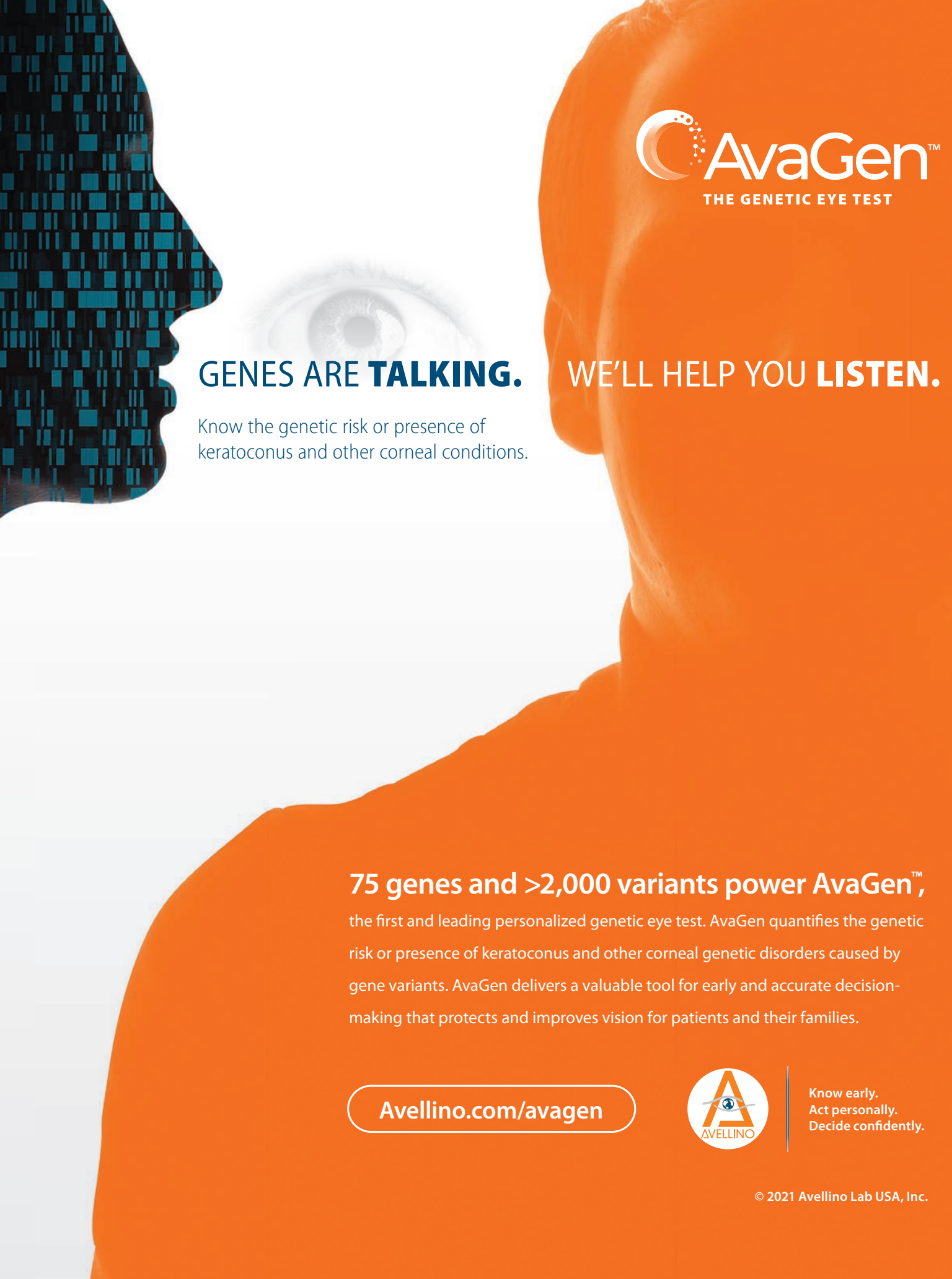
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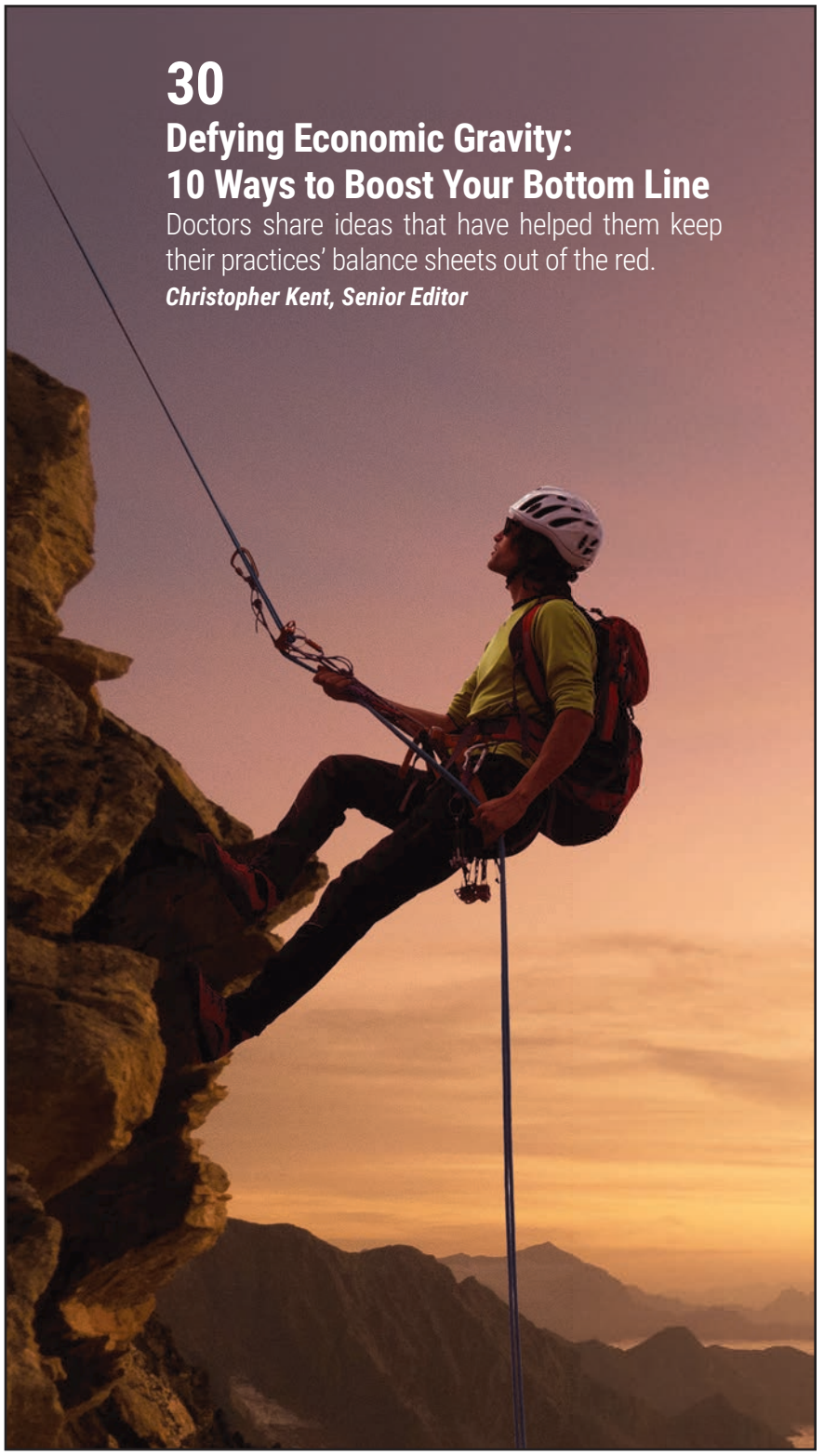

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REFERENCE: 1. Photrexa [package insert]. Waltham, MA: Glaukos, Inc; 2016.

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REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Deep Cuts and Side Hustles

There's a sequence early on in the classic adventure movie *Raiders of the Lost Ark* where the main character, intrepid archaeologist Indiana Jones, sprints through an ancient temple as a giant rolling stone ball threatens to crush him from behind. As he finally bursts through the exit to safety, Indy looks up to see a platoon of warriors aiming poison-tipped arrows at him: Out of the frying pan, into the fire.

Our country's intrepid ophthalmologists find themselves in a similar situation, except now the giant stone ball is 2020—with the pandemic and the cascade of staff furloughs and decreased income—and the enemy warriors are the Centers for Medicare and Medicaid Services, armed with poison-tipped reimbursement cuts set to fire in 2022.

As to what cuts are coming, the American Medical Group Association notes that physicians can expect as much as 10 percent worth of cuts, consisting of a 2-percent Medicare sequester cut, a 4-percent Medicare Pay-As-You-Go reduction and a 3.75-percent decrease in the Medicare conversion factor.[1]

In a survey regarding the potential fallout from these cuts, the AMGA reports that 43 percent of doctors say they'll have to institute hiring freezes or delays, 37 percent will begin eliminating services and 25 percent will furlough or lay off non-clinical staff.[1]

Physicians are also looking into "side hustles," alternative ways to make income, as reimbursements shrink and the pandemic wreaks havoc with their traditional way of practicing and making a living. Medscape reports that nearly 40 percent of doctors now have a job in addition to their medical practice. And, of the doctors who started moonlighting in the past 12 months, 45 percent were driven to it by the pressures put on them by the pandemic.[2] Most of these side jobs are in the medical field, consisting of such things as participating in clinical trials and teaching, but they also include such activities as real estate, playing music and making astrological charts.

In ophthalmology, too, physicians are looking into alternative income, as illustrated by this month's cover story (p. 30). Though not as high-falutin' as crafting psychic star maps, the ideas the surgeons we spoke to can help you make up some of the income that was lost during the pandemic, or which may go away if the 2022 cuts go into effect.

Speaking of going away, one of the most sobering statistics from the AMGA physician survey was that 22 percent of the respondents say they'll stop accepting new Medicare patients as a result of the cuts. This means that, if the government's not careful, it may utimately hurt the people the Medicare program was designed to help in the first place: the patients. ◀

— Walter Bethke
Editor in Chief

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2. Side Gigs: A Growing Trend as Physicians Seek Extra Income. https://www.medscape.com/slideshow/side-gigs-6014093#1. Accessed October 25, 2021.

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Retinal Detachment Repair

(Continued from p. 8)

so fast the corrugations don't have time to resolve."

If you've never seen these folds before, you're not alone. It's not easy to see ORFs, mostly because catching them requires tediously scrolling through every cut of your *en face* OCT volume scan. "If you just look quickly at a five-line raster scan, you won't pick these up," Dr. Muni says. (His group developed a custom segmentation algorithm with high sensitivity for detecting ORFs, making visualization much easier.) Ultimately, he says retina surgeons should be comfortable performing all techniques of RD repair so they can choose the most appropriate procedure for an individual patient.

1. Lee W, Bansal A, Sadda S, et al. Outer retinal folds following pars plana vitrectomy vs. pneumatic retinopexy for retinal detachment repair: Post hoc analysis from PIVOT. Ophthalmol Retina 2021. In Press. [Epub September 11, 2021].
2. Bansal A, Lee W, Felfeli T, Muni R. Real-time in vivo assessment of retinal reattachment in humans using swept-source optical coherence tomography. Am J Ophthalmol 2021;227:265-274.

Slow Taper of Steroids Effective in Postop Iritis

Idiopathic persistent iritis after cataract surgery is a distinct clinical anterior uveitis most common in African-American and female patients. It's characterized by an unexpected onset of iritis after cataract surgery and a high rate of steroid dependency, glaucoma and macular edema. Recent research suggests it's best treated with an initial slow taper of topical steroids, although adjuvant systemic anti-inflammatory therapy may be necessary for remission and complication avoidance.[1]

This retrospective interventional case series included 45 patients with idiopathic persistent iritis after cataract surgery patients (86.7 percent African American, 77.3 percent female) who were evaluated for demographics, clinical characteristics and immune blood markers. Those with more than six months of follow-up were evaluated for treatment efficacy in achieving remission (absence of inflammation for three months), with either exclusive slow tapering of topical steroids or systemic immunosuppression.

Antinuclear antibodies were present in 69.9 percent of patients. The main complications were steroid dependency (84.4 percent), glaucoma (53.5 percent) and macular edema (37.5 percent). The proposed treatment strategy achieved remission in 93.8 percent of the population, with a mean of 6.1 months via tapering of topical steroids in 46.9 percent of patients. However, in 53.1 percent of cases, adjuvant anti-inflammatory systemic medication was indicated. Meloxicam use was associated with remission in 64.7 percent of these patients; in the minority with persistent iritis, treatment was escalated to methotrexate, which was successful in all of the cases.

The authors recommend "a strict systematic treatment with an algorithm which begins with a slow tapering of steroids over two months and, if iritis flares, systemic medication should be introduced, escalating from meloxicam to methotrexate." ◀

1. Soifer M, Mousa HM, Jammal AA, et al. Diagnosis and management of idiopathic persistent iritis after cataract surgery (IPICS). Am J Ophthalmol. October 12, 2021. [Epub ahead of print].

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How to Manage Pediatric MGD

Though adults can also have meibomian gland dysfunction, the stakes can be higher in pediatric MGD.

AMAL AL-LOZI, MD
AND S. GRACE PRAKALAPAKORN, MD, MPH
DURHAM, N.C.

Meibomian gland dysfunction can be troublesome for our adult patients, but it can pose even more hazards for children: Chalazia and corneal scarring from MGD can lead to amblyopia. If you catch the problem in time and treat the patient intensively, however, you can achieve good outcomes.

In this article, we provide an overview of various treatments for meibomian gland dysfunction, blepharokeratoconjunctivitis and chalazia that have been explored in children and summarize specific published regimens.

Defining the Problem

Multiple meibomian glands line the upper and lower eyelid margins and secrete the oily component of tears. Ophthalmologists commonly diagnose and treat meibomian gland dysfunction, characterized by duct obstruction and alteration in the quality of glandular secretions that can lead to a dry, irritated ocular surface.[1] Meibomian gland dysfunction can occur in isolation but can also be associated with blepharokeratoconjunctivitis, which consists of inflammation of the eyelid margin, and conjunctival and corneal inflammation in more severe cases. The most severe cases of BKC can lead to corneal perforation.[2]

MGD can lead to the development of chalazia, sometimes referred to as styes, which are benign nodular eyelid masses defined through tissue analysis to be chronic, sterile and having a characteristic lipogranulomatous inflammatory profile. They form within blocked meibomian glands and have a high recurrence rate in children, ranging from 17 to 67 percent.[3-5] As mentioned earlier, unique complications of chalazia in children include amblyopia secondary to induced corneal astigmatism or mechanical ptosis. Accordingly, aggressive treatment may be needed to preserve vision.

Standard Treatments

Initial treatments are simple and can be done at home. They consist of the following:

• ***Lid scrubs and warm compresses.*** Lid scrubbing aims to remove inflammatory debris and crusts along the anterior lid margin (i.e., along the lash line). Dilute baby shampoo, dilute bicarbonate solution, warm water[6] or commercial lid scrubs can be applied with a cotton-tip swab, clean cloth, or clean fingertips (make sure fingernails are short so as not to scratch the eyelid or ocular surface) to scrub the eyelid margin. Lid scrubbing can be as simple as rubbing the margin of the eyelids with clean fingertips while showering.[5]

Warm compresses can also loosen adherent debris around the eyelash base, but mainly target posterior blepharitis (i.e., inflamed, blocked meibomian glands). Warm compresses melt the dried meibum (i.e., meibomian gland secretions) that causes blockage, immediately after which vertical eyelid massage is needed to express abnormal meibum.[7] Vertical eyelid massage requires firm eyelid pressure applied by a fingertip, with a downward force on the upper eyelid, and an upward force on the lower lid.

Various treatment regimens and materials can be used when applying warm compresses in children. Uncooked rice in a clean sock can be microwaved for 20 to 30 seconds, then applied for five to 10 minutes to each eye, two to four times a day.[8,9] (The caregiver should first ensure the rice is not so warm as to cause skin burns and be aware that microwaves can distribute heat unevenly.)[8] A microwavable moist pack or hard-boiled eggs could also be used.[9,10] It's helpful in young, less-cooperative children to couple warm compresses with a distraction such as television, music or bathing.[9]

• ***Topical and oral antibiotics.*** Topical antibiotics are used to help control bacterial colonization of the eyelid margin, particularly against gram-positive organisms. Bacitracin or erythromycin ointment can be applied on clean eyelid margins at bedtime; these antibiotics are safe options if required chronically.[7] Another option is chloramphenicol drops four times a day and chloramphenicol ointment at bedtime for one month, followed by ointment at bedtime only for two to

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Dr. Collinge is an assistant professor in the Department of Pediatrics of the University of Connecticut School of Medicine. She has no financial interest in any of the products discussed in the article.

To treat ocular inflammation and pain following ophthalmic surgery or ocular itching associated with allergic conjunctivitis.

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

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

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Ocular Inflammation and Pain Following Ophthalmic Surgery

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

Itching Associated with Allergic Conjunctivitis

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: intraocular pressure increased (3%), lacrimation increased (1%), eye discharge (1%), and visual acuity reduced (1%). The most common non-ocular adverse reaction was headache (1%).

Please see adjacent Brief Summary of full Prescribing Information.

*93% (187/201) DEXTENZA patients were satisfied with the insert in the Phase 3 Study for the treatment of ocular inflammation and pain following ophthalmic surgery.[3]

[†]73.6% of physicians in Study 1, 76.4% in Study 2, and 79.6% in Study 3, for the treatment of ocular inflammation and pain following ophthalmic surgery, rated DEXTENZA as easy to insert.[2,5]

References: 1. DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2021. **2.** Tyson SL, et al. *J Cataract Refract Surg*. 2019;45(2):204-212 [erratum in: 2019;45(6):895]. **3.** Data on File 00837. Ocular Therapeutix, Inc. **4.** Sawhney AS, Inventors, et al. Incept, LLC, Assignee. Drug Delivery Through Hydrogel Plugs. US Patent 8,409,606 B2. April 2, 2013. **5.** Walters T, et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11.

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three months.[6]

If the above treatments don't suffice, oral antibiotics may be used to treat MGD—not for their antimicrobial effect, but for the secondary anti-inflammatory properties and lipid modulation effect of certain classes.[8] These are particularly useful in severe pediatric BKC or disease associated with ocular rosacea[11] and can be used as a tool to wean patients off of chronic topical steroids.[12] The most common oral antibiotics used are erythromycin in patients younger than 8 years of age and doxycycline in patients over 8; azithromycin, roxithromycin and minocycline have also been used.[5,6,9,11-14] Tetracyclines are contraindicated in younger children due to teeth discoloration before completion of dentition.[15]

In the literature, erythromycin dosing has ranged from one-quarter to full-strength dosing of 50 mg/kg/day.[9] While erythromycin can cause gastrointestinal side effects, it's generally well-tolerated.[5,9] Others have recommended azithromycin 5 to 15 mg/kg/day.[9] We've found the use of clarithromycin 7.5 mg/kg b.i.d. to be effective and well tolerated. Reported doxycycline regimens include 50 mg b.i.d., followed by prolonged-release doxycycline 40 mg/day for maintenance therapy.[16] Patients should be informed about photosensitivity associated with the use of doxycycline and advised to protect sun-exposed areas of the body.

The duration of oral antibiotics depends on severity. Most patients completed one round of antibiotic therapy within two to seven months, but reports range from one to four years of continual or intermittent use.[9,11,13,14] A response to oral antibiotics is typically seen within two to six weeks.[12-14] A general recommendation is to use oral agents for three to six months, and taper per clinical course[9] to as low a dose as possible without causing recurrent symptoms, even to every-other-day dosing. When treating patients with ocular rosacea, some clinicians suggest treating moderate cases for six months and severe cases for 12 months with oral antibiotics.[16] If topical drops and ointments are not enough to treat relapses, oral antibiotics can be restarted.[12]

• ***Topical tea tree oil.*** *Demodex* mite (*D. folliculorum* and *D. brevis*) infestation of eyelash follicles and meibomian glands is more common in children than previously thought, and can be associated with BKC and recurrent chalazia.[17-19] They're characterized by "cylindrical dandruff" along the eyelash base.[17] Diagnosis may be more difficult due to lack of pediatric cooperation with eyelash epilation used to identify mites; however, diagnosis and treatment of *Demodex* should be considered in refractory cases of pediatric BKC.[17]

Due to its active ingredient, terpinen-4-ol, tea tree oil is the treatment for *Demodex*-associated lid margin disease.[20] One group saw subjective improvement of symptoms (i.e., eyelid swelling, redness) after one week in all patients and full resolution of symptoms after three months using the treatment regimens outlined in Table 1 (p. 22).[17] In this

study, one patient had a recurrent episode of BKC that resolved with a second round of treatment.[17] It's recommended to use this regimen for six weeks to cover two life cycles of the mite,[21] but four weeks of treatment has also been successful.[17]

While tea tree oil alone is the standard treatment for *Demodex*, one group combined tea tree oil treatment with ivermectin (two doses, 200 µg/kg, one week apart) for microscopically-proven *Demodex*-associated BKC, leading to clinical improvement in all pediatric patients after three months.[18]

• ***Omega-3 essential fatty acids.*** Omega-3 essential fatty acids are an essential component of meibum. Their supplementation is thought to decrease meibomian gland blockage by creating an anti-inflammatory environment at the eyelid margin and by improving the quality of meibum.[22]

Some providers have used flaxseed oil as a means of omega-3 fatty acid supplementation in children.[5,8] One observational study reported success using flaxseed oil as maintenance therapy for pediatric BKC after initial intervention with oral antibiotics.[5] Suggested regimens include 2.5 mL (one teaspoonful) daily[5,8] and reducing administration to alternate days if possible.[5] If capsules of flaxseed oil are too large to swallow, they can be broken and sprinkled onto food. Alternatively, ground seeds can also be used.[8] Based on opinion alone, one group recommended not exceeding six months of use due to lack of data on chronic use of flaxseed oil in children.[5]

Treatments Specific to BKC

When inflammation is involved, the following treatments have proven useful.

• ***Topical steroids.*** While topical steroids are useful for initial control of acute inflammation or relapse, patients need to be monitored closely due to intraocular pressure spikes. Steroid-induced ocular hypertension occurs more frequently in children than adults, especially under 10 years of age, and can occur as early as one week after initiation of use three to four times daily.[23,24] Topical steroid duration might be expected to last between one and 16 months, with many patients requiring intermittent treatments for more than six months.[5] When using steroids, it's best to taper to the lowest dose that allows for inflammatory control, to discontinue as soon as possible and to use steroids that are less likely to cause an increase in intraocular pressure, such as fluorometholone.[7]

• ***Steroid-sparing immunomodulators.*** In patients with keratitis or corneal scarring secondary to blepharokeratoconjunctivitis, topical cyclosporine A may be a useful maintenance therapy after initial control with topical steroids, due to the long-term side effects of steroids.[16,25] One group had sustained control of disease in eight of 11 children over an average treatment period of 13 months using cyclosporine 2% q.i.d.[25]

TABLE 1. SPECIFIC REGIMENS FOR VARIOUS TREATMENTS OF BKC AND CHALAZIA

Source	Treatment	Use	Description of regimen
American Association of Pediatric Ophthalmology and Strabismus*	Lid scrubbing technique	Any case of meibomian gland dysfunction	Wash hands thoroughly with soap and water. Apply mild diluted shampoo (typically baby shampoo) or lid scrub solution to a clean cloth and work into a lather. After closing the eyes, gently scrub the lashes and eyelid margin vertically and horizontally with the soapy cloth. Rinse eyes and face with water.
Liang et al. 2010	Eyelid scrub with 50% tea tree oil	*Demodex*	Three times daily for four to six weeks Scrub upper and lower lash roots, using six strokes per eyelid, with a cotton tip wetted with tea tree oil. Five minutes later, clean eyelids with a dry cotton tip applicator to loosen dandruff.
Liang et al. 2010	Eyelid massage with 5% tea tree oil ointment (used for less-cooperative patients)	*Demodex*	Twice daily for four to six weeks Wash face and eyelids with baby shampoo or soap. Rinse face and eyelids with warm water. Apply small amount of 5% tea tree oil ointment to both index fingers. With patient's eyes closed, massage eyelid margins from one end to another for five minutes. Leave ointment on without washing.
Viswalingan et al. 2005**	Erythromycin+	Moderate to severe BKC	30 to 40 mg/kg/day divided in three doses for three weeks Taper to twice daily for four to six weeks.
Choi et al. 2013++	Azithromycin	Recurrent BKC	5 mg/kg daily for six to 10 weeks, then every other day for four weeks

* https://aapos.org/glossary/blepharitis
** Was used in moderately severe or severe cases; combined with various other treatments in this study including lid hygiene, topical antibiotics.
+ Note that other studies had varied duration and dosing of erythromycin on a case-by-case basis.
++ This study combined azithromycin with lid hygiene and topical cyclosporine.

Treatments Specific to Chalazia

When glands are blocked, the following interventions are effective.

• ***Intralesional steroid injection.*** For recurrent, non-resolving or multiple chalazia refractory to the above treatments, intralesional steroid injection is an option. Studies have demonstrated the success of intralesional triamcinolone injection in children with chalazia. One study showed an average time to resolution of 18.2 days after injection of an average of 3.5 mg of triamcinolone.[10] Another study demonstrated resolution of chalazia within two to four weeks in 75 percent of patients, and resolution in 100 percent of patients, with one to two additional injections.[3] Intralesional triamcinolone can be injected subcutaneously or, if the eyelid isn't too swollen to be inverted, subconjunctivally.

Advantages of intralesional steroid injection, compared to incision and curettage, include less bleeding and scarring, ability to perform simultaneously on multiple chalazia, and ability to inject close to the lacrimal punctum.[10] These advantages should be weighed against the risks of globe perforation, retinal or choroidal vascular occlusions, and possible skin depigmentation (with a higher risk in darker skin tones).[10]

• ***Incision and curettage.*** This can be considered for chalazia that don't respond to the above treatments. In many children, this procedure will have to be performed under general anesthesia. One small study in children demonstrated 75-percent success after first incision and curettage and 100-percent resolution after a second procedure; two cases had recurrence within one month of resolution.[3] They also showed a 100-percent success rate after combined intralesional triamcinolone acetonide and incision with curettage.[3] Despite high success, using the above treatments to prevent recurrent chalazia should be continued.

On the Horizon

New treatments for BKC and chalazia continue to appear. Based on evidence that the intestinal microbiome modulates ocular inflammatory disease,[26] one study found that oral probiotics with conservative treatment versus conservative treatment alone led to faster resolution of chalazia (28 versus 54 days) in children.[27] More research is required for these preliminary findings, but we expect the treatment landscape to evolve in years to come. ◀

(Continued on p. 24)

ABOUT THE AUTHORS

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(Continued from p. 22)

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Chaos Theory

Musings on life, ophthalmology and the practice of medicine.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

Physics tells us that, from a very fundamental point of view, all properties and processes in this universe trend toward disorder, less energy, chaos. And a key process describing these systems is entropy, the degree of a system's randomness or disorder. Entropy is a loss of useful energy and, unfortunately, it keeps increasing. This is the natural way of the universe—unless we push back.

This concept of the universe trending toward chaos comes to mind when bad things happen, when order breaks down. Of course, there are days when we feel we've changed the world—or at least someone's small corner of it. And then there are days when we feel if not crushed, at least defeated. "Why even get out of bed?" we think. On those days, we start to wonder if we're the only ones who care. It's easy to think no one else does. But, despite these feelings, most of us still set an alarm, get dressed and go do what we've always done: See patients, restore sight, take care of our families and our friends. It's an endless process that really revolves around creating order out of chaos, evoking a more perfect state from a less perfect one, decreasing entropy.

But why do we feel the need to bring order to things?

We constantly work to make our lives and the environment around us more orderly. We create reason, logic, forward motion. It's in our DNA.

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Personally, I'm one of those many people that can't stand a mess, disorder or unfinished business. I suppose it's a variation of being obsessive/compulsive, which a lot of ophthalmologists are. "A place for everything and everything in its place," as they say. Beyond any OCD issues, I think bringing order to chaos is a basic drive of human beings. It's how we make our mark on the world: Since chaos and disorder are the natural state of things, creating organization is a sign that we were here. (It also feels good.)

At the same time, we have to acknowledge that we're pushing that rock up the hill time after time with no end in sight, and our achievement is only temporary. If we stopped pushing, as physics peskily reminds us, the universe would, on its own, move toward darkness and disorder—a very depressing realization. But what should we do with the rock, then? Stop pushing it? Just give up? Clearly not, although at times in our lives, and at various times in human history, it's tough to acknowledge that. Often, it can be hard to see a way forward to a lighter, happier, more ordered life.

I think it's probably a truism that, at times, we view our own lives through the lenses of adversity and hopelessness. Certainly, COVID and the current political climate can make us see things that way. But stop for a second and imagine what the world looked like to those living through other challenging times, such as the Second World War. At that time, with the entire world seemingly on fire, one couldn't imagine a worse chance of staving off entropy—you could practically smell it in the air—yet they did. And we will, as well. Over the many millennia of human history, humans overcame chaos and hopelessness. Terrible times always eventually yielded to better ones, and ultimately led to the advancement of civilization—although at the moment it was probably hard to see exactly how. With that perspective on history, we should all take heart: While we'll never win the war on entropy, we can create windows of wonder and order—if we only try. ◀

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

PAUL M. LARSON, MBA, MMSC, COMT, COE, CPC, CPMA

MEDICARE Q&A

The Fall Updates You Need to Know About

A look at the most recent updates to QPP/MIPS, CMS audits and 2022 ICD-10.

Medicare recently found two scoring errors related to the QPP/MIPS 2020 data which might affect you in a few months, and also changed the Cost scoring for this past year (remember that 2020 scoring affects your 2022 payments). There are also some changes to 2021 reporting that, though they might not impact every provider, in some cases you'll have some decisions to make as we enter the last quarter of 2021. Even though the pandemic regulations are still in place, CMS has also instructed the MACs to re-start some of the audits that were on pause for that reason. Lastly, we discuss the (very) few changes to ICD-10-CM for 2022.

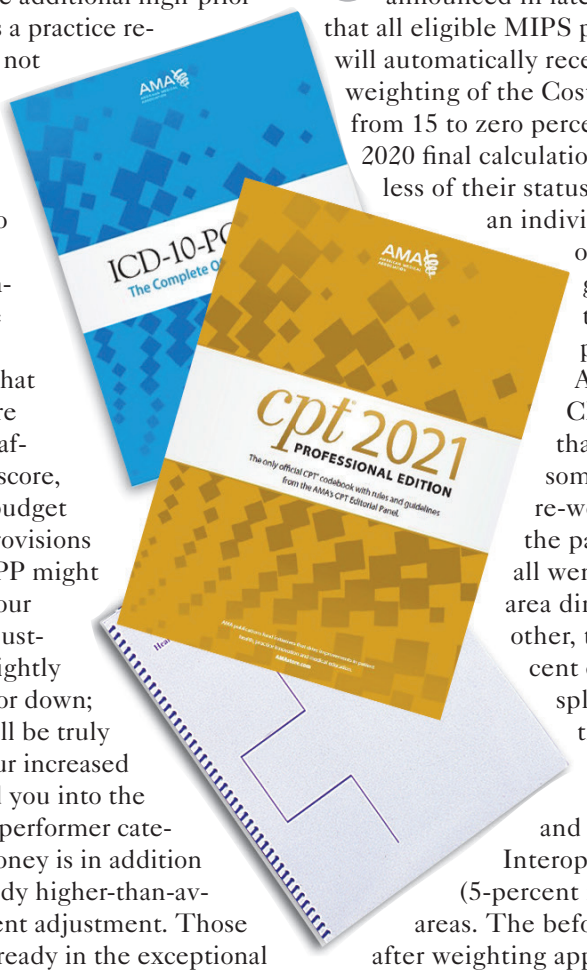
Q What changes has CMS made to QPP/MIPS for 2020 scoring?

A On September 27, CMS noted that eye doctors might see some changes to their 2022 payment and performance adjustments. They found two errors. One is only for those providers enrolled in a Medicare Shared Savings Program or Accountable Care Organization; CMS found that in some cases they might not have attributed up to 10 complex patient bonus points. This means that CMS didn't give the points they should have, so scores can only go up.

The other change affects only those who reported more than one "high priority" quality measure. CMS' error was that the bonus points for the additional high-priority measures a practice reported were not credited, so scores can only go up and no scores can go down.

The downside to some QPP scores going up is that even if you're not directly affected via a score, the overall budget neutrality provisions built into QPP might mean that your payment adjustments are slightly affected up or down; but these will be truly minor. If your increased score moved you into the exceptional performer category, that money is in addition to your already higher-than-average payment adjustment. Those who were already in the exceptional performer category but had no score change might see a slight dilution in their particular bonus due the effect on the pool of funds being spread further.

If you feel your score for 2022 is still incorrect, due to the changes above, CMS extended the appeal timeline—you now have until 8 PM Eastern on November 29 to request a targeted review.



Q What about the Cost category? My practice was closed or ran a severely reduced schedule for part of the year.

A This is also good news. CMS announced in late summer that all eligible MIPS providers will automatically receive re-weighting of the Cost category from 15 to zero percent in their 2020 final calculation, regardless of their status in MIPS as an individual, group or virtual group, or their participation in an APM Entity. CMS noted that unlike some other re-weighting in the past, where it all went from one area directly to another, this 15-percent change is split between the Quality (10-percent increase) and Program Interoperability (5-percent increase) areas. The before-and-after weighting appear in the

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INDICATION

Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1% is indicated for the treatment of acquired blepharoptosis in adults.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- Acquired ptosis may be associated with neurologic or orbital diseases such as stroke and/or cerebral aneurysm, Horner syndrome, myasthenia gravis, external ophthalmoplegia, orbital infection and orbital masses. Consideration should be given to these conditions in the presence of acquired ptosis with decreased levator muscle function and/or other neurologic signs.
- Alpha-adrenergic agonists as a class may impact blood pressure. Advise Upneeq patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to seek medical care if their condition worsens.
- Use Upneeq with caution in patients with cerebral or coronary insufficiency or Sjögren's syndrome. Advise patients to seek medical care if signs and symptoms of potentiation of vascular insufficiency develop.
- Upneeq may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute narrow-angle glaucoma develop.
- Patients should not touch the tip of the single patient-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

ADVERSE REACTIONS

Adverse reactions that occurred in 1-5% of subjects treated with Upneeq were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation, and headache.

DRUG INTERACTIONS

- Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta blockers, anti-hypertensives, and/or cardiac glycosides is advised. Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.
- Caution is advised in patients taking monoamine oxidase inhibitors which can affect the metabolism and uptake of circulating amines.

To report SUSPECTED ADVERSE REACTIONS or product complaints, contact RVL Pharmaceuticals at 1-877-482-3788. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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

RVL PHARMACEUTICALS, INC.

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Bridgewater, NJ 08807
Customer Service 1-866-600-4799

PM-US-UPN-0197-2 06/21

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UPNEEQ®
(oxymetazoline hydrochloride ophthalmic solution), 0.1%

Eye-Opening Possibilities

UPNEEQ® (oxymetazoline hydrochloride ophthalmic solution), 0.1%, for topical ophthalmic use

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ptosis as Presenting Sign of Serious Neurologic Disease

Ptosis may be associated with neurologic or orbital diseases such as stroke and/or cerebral aneurysm, Horner syndrome, myasthenia gravis, external ophthalmoplegia, orbital infection and orbital masses. Consideration should be given to these conditions in the presence of ptosis with decreased levator muscle function and/or other neurologic signs.

5.2 Potential Impacts on Cardiovascular Disease

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

5.3 Potentiation of Vascular Insufficiency

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

5.4 Risk of Angle Closure Glaucoma

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

5.5 Risk of Contamination

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

7 DRUG INTERACTIONS

7.1 Anti-hypertensives/Cardiac Glycosides

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

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

7.2 Monoamine Oxidase Inhibitors

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on UPNEEQ use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 7 and 278 times the maximum recommended human ophthalmic dose (MRHOD), respectively, based on dose comparison. [see Data]. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

RVL PHARMACEUTICALS, INC.

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

PM-US-UPN-0203 01/21

RESULT OF RE-WEIGHTING THE COST CATEGORY

	Quality	Cost	Improvement Activities	Program Interoperability
2020 Before	45%	15%	15%	25%
2020 Now	55%	0%	15%	30%

table above. If a practice has other re-weighting from hardship exceptions, CMS notes that those will remain in effect and this split from Cost re-weighting is additive.

Q I was in an area that was affected by Hurricane Ida. Is there anything that can help me in 2021?

A Yes. Those in the affected areas (New York, New Jersey, Louisiana, most of Mississippi and parts of Pennsylvania) will now be automatically identified by their billing ZIP code and will receive no negative adjustment in 2023. This new declaration is in addition to the waivers already in place due to the COVID-19 public health emergency (PHE). As with other "Extreme and Uncontrollable Circumstance" hardship exceptions, if you are affected but choose to submit MIPS data anyway in two or more MIPS categories for the 2021 reporting year, you will be scored and receive the adjustment.

Q You mentioned TPE audits. What are those?

A This is a special type of audit with education afterwards. CMS announced in an August issue of the "MLNConnects" newsletter for the Medicare Learning Network (https://www.cms.gov/files/document/2021-08-12-mlnc.pdf) that Targeted Probe and Educate (TPE) audits would resume again after being paused as part of the COVID-19 pandemic.

CMS notes on the TPE webpage (www.cms.gov/Research-Statistics-Data-and-Systems/Monitoring-Programs/Medicare-FFS-Compliance-Programs/Medical-Review/Targeted-Probe-and-EducateTPE) the following information:

• CMS' Targeted Probe and Educate program is designed to help providers and suppliers reduce claim denials and appeals through one-on-one help.

• MACs use data analysis to identify:

> **"In the unusual situation in which you do actually encounter a condition that requires a new [ICD-10-CM] code, you must use these new codes as of October 1, 2021."**

— providers and suppliers who have high claim error rates or unusual billing practices; and

— items and services that have high national error rates and are a financial risk to Medicare.

• Providers whose claims are compliant with Medicare policy won't be chosen for Targeted Probe and Educate.

• [This type of audit] "typically involves the review of 20 to 40 claims per provider/supplier, per item or service. This is considered a round, and the provider/supplier has a total of up to three rounds of review.

"After each round, providers/suppliers are offered individualized education based on the results of their reviews. Providers/suppliers are also offered individualized education during a round when errors that can be easily resolved are identified."

Q Any changes to ICD-10-CM for 2022?

A Yes, but they're very minor and won't likely affect you much at all.

In the unusual situation in which you do actually encounter a condition that requires a new code, you must use the new codes as of October 1, 2021; don't delay until January 2022 just because the "code year" says 2022.

Our specialty's chapter of the ICD-10 code manual, (Chapter 7: Diseases of the Eye and Adnexa) had one minor change: Eliminating an improper "dash" on code I10 that you wouldn't use on claims anyway.

Chapter 19 (Injury, Poisoning & Certain Other Consequences of External Causes) had similar changes to S00.1 (Contusion of eyelid and periocular area) and S01.0 (Open wound of scalp).

Chapter 12 (Diseases of the Skin and Subcutaneous Tissue) has a few changes that we actually might encounter when the skin is irritated. That change under L24 (Irritant contact dermatitis) is:

• Add: L24.A Irritant contact dermatitis due to friction or contact with body fluids

— Add: L24.A9 Irritant contact dermatitis due to friction or contact with other specified body fluids

In Chapters 13 (Diseases of the Musculoskeletal System & Connective Tissue) and 18 (Symptoms and Signs), the term that was previously used in the ICD-10 manual, "Sicca syndrome," was replaced by the term "Sjögren syndrome" for M35.01 codes.

Chapter 20 (the strange chapter with all the external causes of morbidity) had lots of changes that don't affect you unless your specific state Medicaid program requires their use—and even that would be rare, as most states' programs don't ask for or require them. ◀

DEFYING ECONOMIC GRAVITY: 10 WAYS TO BOOST INCOME

Most ophthalmologists are working harder but earning less. Here, doctors share ideas that have helped them keep their practices' balance sheets out of the red.

CHRISTOPHER KENT
SENIOR EDITOR

It's often said that death and taxes are inevitable, but today—if you're an ophthalmologist—you might add "declining reimbursements" to that list. This economic reality has forced doctors to seek out new ways to generate income to keep their practices economically viable.

John S. Jarstad, MD, FAAO, a professor of clinical ophthalmology at the Morsani School of Medicine, University of South Florida-Tampa, recalls the first time he really felt the economic crunch, back in the 1990s, when Medicare quit paying physicians for a few months. "We had to scramble to come up with ideas to immediately generate cash flow," he recalls. "Yes, we knew we could work harder and longer hours, but my office administrator suggested we try working smarter, by promoting options that could bring in more profitability while we did the same amount of work."

Here, in that spirit, ophthalmologists offer some of the best ideas they've encountered for keeping a practice economically viable.

1 ***Make sure your facilities are always being used.*** To survive tough economic times, you need to make the most of your existing resources. That includes making sure the physical plant you work in continues to generate income nearly every day. In a large practice, that may not be a problem, but for a solo ophthalmologist it can be tough to manage. The simplest solution is to add either more partners to the practice or one or more optometrists.

"The bottom line is that your surgical patients originate from your office," notes Richard L. Lindstrom, MD, founder and attending surgeon emeritus at Minnesota Eye Consultants in Bloomington, Minnesota. "If your office sees more patients—whether because you're seeing more patients yourself, or because other doctors are seeing patients when you're not in the office—you'll have more surgery to do."

Dr. Lindstrom suggests that, based on his experience, the ideal size for a small practice is four MDs, with two to four optometrists also on staff and a practice-owned ASC or in-office surgical suite. He explains the rationale for this arrangement: "With this practice configuration, one of the doctors can be in the OR every day, leaving two or three doctors working in the clinic all the time. That works even if one doctor is on vacation or away at a meeting, and you can have the doctors take turns attending meetings. This keeps all of your facilities in constant use, and everyone can take time off without disrupting the routine.

"Of course, you can go bigger," he adds. "I currently have 29 doctor associates. But the sweet spot was when there were four of us."

The other option, which many ophthalmologists have chosen, is to bring one or more optometrists into the practice. "At Durrie Vision we've always integrated ophthalmology and optometry, and it works very well," says Daniel S. Durrie, founder of Durrie Vision in Overland Park, Kansas. "Our surgeons do the surgery and all of our own preop exams, but many postop exams and routine visits can be handled by the optom-

This article has no commercial sponsorship.

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

etrists. They're an integral part of the practice, and as we move along and the volume of cataract surgery goes up, I think adding optometric services—under the direction of a physician—makes a lot of sense."

Dr. Jarstad recounts that when he started out as a solo practitioner, he hired Bradley A. Frederickson, OD, to help him keep his office open more hours than he could manage while he was transitioning from academia to private practice. Eventually, he and Dr. Frederickson were managing the practice full time. "Dr. Frederickson had completed a one-year 'fellowship' with a cataract and refractive surgeon, and had exceptional clinical and people skills," he recalls. "It quickly became clear that he was excellent at performing screenings and medical eye exams, and that took quite a load off of my incredibly busy schedule.

When Washington State became one of the early states to allow optometrists prescribing privileges, Dr. Jarstad "expanded Dr. Frederickson's scope of practice to include management of stable medical glaucoma patients, diabetic eye screenings, triage of patients with cornea abrasions and other eye injuries, as well as managing postop patients who had concerns when I was in our surgery center operating. Eventually, unless a patient specifically requested one of our surgeons, we triaged all new patients through Dr. Frederickson.

"We added a second optometrist as the practice grew, which added better immediate access for our patients and also added to our bottom line," he notes. Dr Jarstad says that bringing in the right optometrists not only served his clinic's patients but also relieved a significant amount of daily stress.

Dr. Frederickson, who has practiced at the Evergreen Eye Center for about 28 years, explains that the optometrists in the practice maximize opportunity costs for the surgeons by managing all non-surgical

Bradley A. Frederickson, OD

Adding optometrists to your practice can ensure that facilities are always in use, free you to do more surgery and be a significant source of referrals.

ocular pathology. "Having a well-trained OD manage these patients frees up the surgeon to concentrate on surgical cases," he notes, "while generating new patients for the surgeon to treat.

"The other alternative is to have an optical in the practice that offers routine eye exams, glasses and contact lenses," he continues. "We don't offer routine eye exams or sell glasses in our practice, but I know some ODs work in large ophthalmological clinics and generate revenue through the practice's optical department, offering routine exams and so forth. They increase the practice's patient base and can generate referrals within the practice."

In terms of hiring an optometrist, Dr. Frederickson notes that not every optometrist will have the skillset a surgical practice may need. "If you're going to have the optometrist manage medical issues and postop care, you want to hire a residency-trained OD, or someone who's making a lateral move from another similar practice," he says. "You want someone who's ready to hit the ground running, able to handle all nonsurgical pathology—identification, diagnosis, proper referral to tertiary care, etc. Everyone learns as they go, of course, and every practice will have its own in-house technology and outcomes. But a residency-trained OD is more likely to be ready to deal with medical and surgical patients. That person can be a real asset to the practice."

2 *Offer new patients a baseline widefield retinal photo.*

James J. Salz, MD, in private practice and a clinical professor of ophthalmology at the University of Southern California Los Angeles, offers widefield retinal photos to all new patients, as both a retina screening test and a baseline for future comparisons. He says it's beneficial for the patient and a good source of income for the practice—and he notes that most patients are happy to participate.

Dr. Salz explains that patients pay out of pocket to have the photo taken and reviewed by the doctor. "Medicare and insurance companies pay for photographs of pathology such as a retinal hemorrhage, vein occlusion, optic atrophy or diabetic retinopathy," he says. "However, insurance companies consider a photograph of a normal retina to be a screening examination, so patients have to pay for it themselves.

"We explain to the patient that we can take a digital photo of the eye that will be a useful permanent record of their retina," he continues. "It's a more thorough exam than we can do with other instruments, because it generates a digital image that allows us to zoom in and look more closely at areas of interest. However, we also explain that insurance doesn't cover this because we're not monitoring a known health problem. We charge the patient $75 to take and interpret the photo—the same amount we charge for a refraction, another noncovered service. Of course, each ophthalmologist can decide what to charge.

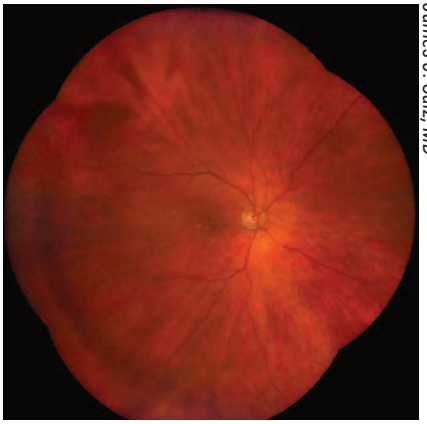
"The technician explains this option to the patient first," Dr. Salz says. "Then, if the patient isn't sure about whether it's worth doing, I show them printed-out examples illustrating the kinds of problems such a photo can reveal, and explain why we think it's an important thing to do. We can find signs of high

blood pressure; we may find cholesterol deposits in the arteries; we can find choroidal nevi; we can find diabetic hemorrhages; and we can find early signs of macular degeneration. These would probably be missed on a routine exam, because on a routine exam there's no magnification."

Dr. Salz says that when explaining this to the patient, he uses the analogy of a physical exam done by their primary physician. "I point out that if they go to their medical doctor for a complete exam, it usually includes a chest X-ray, even if the patient has no complaint," he says. "The only thing the doctor learns from most chest X-rays is that the patient has a normal-size heart and doesn't have lung cancer. This is similar; we're checking to make sure there's nothing wrong with the patient's retina, while creating a baseline for future comparisons. Of course, I tell the patient that when we take the picture, we don't want to find anything! Patients are very happy if they find out that their retina is normal."

Dr. Salz says that patients rarely choose not to have the picture taken. "I'd say 80 to 90 percent of the patients we present with this idea are happy to do it, and they pay for it on the day of the visit," he notes. "The fact that the picture can be taken without touching the eye is an added benefit, especially during a pandemic. The patient signs a basic informed consent, which was suggested by one of the coding experts at the American Academy of Ophthalmology.

"Once the patient has signed the consent we usually have the technician take the picture," he continues. "Both eyes can be photographed in about five minutes, without any need for bright lights or eye contact. Then, when the patient comes into the exam room to see the ophthalmologist, the picture is already loaded onto the computer. We have 24-inch flat-screen monitors in every exam room, so we can show the picture and go over the details with the patient. Patients love seeing their own retina. If the patient has a smartphone, we can also transfer the image to the phone for further perusal by the patient."



James J. Salz, MD

A baseline widefield retinal photograph, paid for by the patient, may uncover retinal issues.

But do these images actually help catch retinal problems? "We find something we didn't expect to find in at least 30 percent of cases," Dr. Salz says. "For example, in one patient we found a cholesterol plaque in an artery that we would have missed on a normal exam. We referred that patient to a vascular surgeon. The vascular doctor found that the patient had carotid artery disease and needed a surgical procedure to clean out the carotid artery. So taking this photo can sometimes be lifesaving.

"It's true that a problem this serious only turns up maybe 5 percent of the time, but we often find something less dangerous that's still important to know about for the health of the eye," he continues. "For example, we commonly find something like fine drusen near the macula, a possible indicator that the patient could develop macular degeneration in the future. That's serious, but not life-threatening. This is good for the patient, because the earlier we diagnose this, the earlier we can put patients on appropriate multivitamins."

Dr. Salz says there are currently at least three companies selling an instrument capable of taking widefield retinal photos. "We own a Zeiss Clarus, which we find easy to use, but Optos and iCare also sell instruments that can do this—the Optomap and Eidon," he points out. "They're all priced in the neighborhood of $50,000 to $80,000. We've found that it's an excellent investment; it pays for itself many times over via the income you generate. Not only can you use it for the patient-paid screening photos, you can use it in the care of diabetics, patients with macular degeneration and so forth, and those pictures are reimbursable. We paid off the cost of the camera within three years.

"If you're not doing this, you're missing a significant source of income, and it definitely benefits the patient," he concludes. "You're not just getting extra income for the practice, you're providing better medical care by finding medical issues that you otherwise would have missed. And of course, if we do find something on the photo—let's say we find a choroidal nevus on the retina—then the picture we take the following year will be covered by insurance, because now the patient has a known pathology."

3 ***Consider sharing the ownership of an ASC.*** "Some doctors are fiercely independent and want to remain solo," notes Dr. Lindstrom. "That makes it almost impossible to make a profit owning an ASC, because an ASC is only financially feasible if it's being used most of the time. To make an OR feasible, whether it's in the office or in an ASC, requires at least 600 procedures a year. If you're operating about 40 weeks a year, that's 15 cases a week. To make an ASC really profitable takes about 1,000 cases a year. So if a typical ophthalmologist does 500 cases a year, the best way to make an ASC work is to have two doctors get together. If you have four doctors, the ASC can become the most lucrative thing in

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the practice. But if you're working solo and doing 500 cases a year, you'll have a hard time making money with your own ASC.

"On the other hand, you can work around this and remain solo by sharing in the ownership of an ASC that's also used by other groups," he says. "Howard Fine's practice shared an ASC with three other independent groups practicing in the same building. This practice model can allow you to enjoy the financial benefits of an ASC without worrying about having enough procedure volume to make it economically feasible.

"If you're interested in pursuing an ASC, you may be able to get useful information about how to proceed just by talking to a surgeon who owns one," he adds. "Alternatively, the Outpatient Ophthalmic Surgery Society—OOSS—is a great source of information on that topic."

4 ***Network with local optometrists to generate referrals.*** Actively marketing your surgical services to local optometrists can result in a reliable stream of referrals for surgery. Having one or more optometrists in your practice can help make this work.

Dr. Jarstad notes that Dr. Frederickson became an important liaison with other optometric providers. "He was instrumental in helping us break into optometric referrals for cataract and LASIK surgery," notes Dr. Jarstad. "He assisted in gaining optometric CE credit for our EyeMD lecture series to our referring optometry base, culminating in more than 100 ODs in our referral network, leading to more than $1 million in yearly optometric referrals for surgeries and clinic visits. That became 8 percent of our total yearly clinic income."

"If you also want referrals from outside ODs to maximize your surgical volume, the ODs in your practice can serve as facilitators between the surgeons and other optometrists in the community," agrees Dr. Frederickson. "Essentially, you're marketing your subspecialty to the ODs in your area. That's likely to be the highest-volume generator for any ophthalmology practice.

"Getting outside referrals doesn't mean less work for the optometrists in the practice, because a lot of the outside ODs don't comanage," Dr. Frederickson notes. "We actually have a two-tiered system. We have a co-management system, where the referring ODs want to manage their patients postoperatively, and are capable of doing so. I don't really see those patients; the surgeons deal with them. But many ODs don't want to comanage, so we'll see their patients postop. They may just want to see the patient back for routine diabetic eye checks. We call that arrangement 'shared care.' Meanwhile, I see plenty of medical visits that are reimbursed by insurance; plus, I'm managing postoperative care and I'm a liaison for the ODs in our area."

Dr. Frederickson explains how their referral network is developed and maintained. "All of us touch base with the local ODs and build relationships with them," he notes. "We provide continuing education opportunities for local optometrists and provide help for their patients. Because of COVID, we now offer CE via Zoom, but we used to meet for dinners and have approved CE presentations that allowed the attendees to accumulate education credits, which they need. This is a great perk to offer if you want to attract and maintain referring ODs outside of your practice.

"Basically," he concludes, "if you want to work with optometrists, you have to be OD-friendly and want their business. It's a symbiotic relationship—a little like the relationship between a dentist and an oral surgeon. An oral surgeon may build relationships with lots of dentists in the area, who then send patients to him. Routine care goes back to the dentist."

5 ***Consider setting up a surgical suite in your office.*** Dr. Durrie is the chairman of iOR Partners, a company dedicated to helping ophthalmologists set up an in-office surgical suite. "Moving surgical suites into the office is definitely a trend," he says. "Our company now has more than 20 centers signed up. Some are doing retina and glaucoma or cornea; most do cataracts.

"I was involved in the trend of moving cataract surgery


Daniel S. Durrie, MD

An in-office surgical suite may enhance revenue and increase your control over your schedule while benefiting patients, proponents say.

from the hospital to the ASC," he continues. "That worked great for ophthalmologists. It gave doctors control of their schedule, and there was revenue to be made if you were owner or part-owner of the ASC. Point of service changes are a trend in other medical specialties as well; orthopedics and cardiology are also moving to ASCs instead of the hospital.

"The latest trend is to take this idea further, creating a surgical suite in your office," he says. "The shift toward having an in-office surgical suite has been happening for more than 10 years, but it's picked up momentum lately. The number of centers we're working with has more than doubled this year.

"Moving your surgical suite into your office has multiple benefits," he points out. "First, it gives you even more control over your schedule. Second, it creates greater efficiency because it uses your staff and your space. For example, the surgical volume for most of the doctors in our center who attended the recent ASCRS meeting actually went up; everyone was able to adjust their surgery schedules to make up for the time away. Third, the revenue that normally went to the ASC now goes to your practice. Fourth, patients love it. They come to the same parking lot, check in at the same front desk, see the same people and then get the surgery done. It makes it more like LASIK, which is done in the office.

"Fifth," he continues, "it has the same level of safety; the surgeon, sterility and equipment are the same as they would be in an ASC or the hospital, and there's published data confirming the safety of this option.[1] Sixth, in-office suites often contain the most cutting-edge, up-to-date equipment, because the surgeon gets to choose the equipment. In addition, we're working to make the end result as environmentally friendly as possible.

"Another advantage is that a practice can do this with a lower volume of cases than you would need in order to justify building an ASC," he says. "To justify having an ASC you need several partners and a high case volume, but an in-office surgical suite works for surgeons doing in the range of 30 to 40 procedures per month. That would never be enough to make an ASC financially feasible."

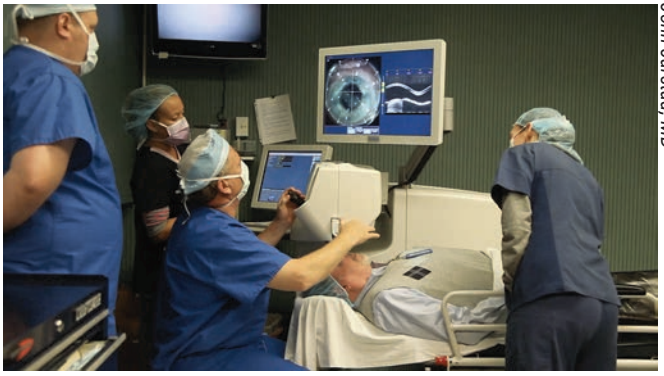
Dr. Lindstrom, who is on the board of iOR, agrees. "An in-office surgical suite provides an option for ophthalmologists who can't afford to build an ASC or aren't allowed to because of certificate-of-need laws," he says. "Doing this allows ophthalmologists to participate on the facility side, and it's more efficient and patient-friendly than most hospitals. In an office-based surgical suite, the ophthalmologist might be able to net $150 per cataract case. You could do better than that with an ASC, but the ASC costs a lot more to build and you need a higher volume to support it, and there are a lot more rules and regulations."

Dr. Durrie adds that it can be hard to set up an in-office surgery center on your own. "People don't know how to get accredited and paid, or how to train the staff," he says. "So, an outside company can be valuable; it's like having a management company run your ASC, except that the OR is in your office."

6 Provide packaged preop cataract surgery medications. "This can help patients by saving them a trip to the pharmacy," Dr. Durrie points out. "Right now most practices write prescriptions; then the patient goes to the pharmacy and gets the preop medications. However, you can have an outside company put the medications together in a package that's either delivered to the patient's home or to a pharmacy near the patient. The companies make sure that all state regulations are followed. It's convenient for the patient, it ensures that the pharmacy won't make substitutions, and there's some potential revenue to be made." Will this cost the patient more? "Not necessarily,"

says Dr. Durrie. "In many cases it ends up costing the patients less than going to the pharmacy."

As an example, one such company is Legrande Health (legrandehealth.com). According to its website, Legrande manages prior authorizations, finds the best prices and arranges delivery to the patient. The company claims that this reduces callbacks to your office by as much as 80 percent.



John Jarstad, MD

Offering premium options, whether presbyopia-correcting lenses or the use of a femtosecond laser, is a time-honored way to increase practice income.

7 Do more premium surgery. Of course, this is an option most surgeons are well aware of. "There's no question you can increase your revenue by doing more premium surgery—especially by treating presbyopia," Dr. Durrie points out. "It's true that you have to make some adjustments to your practice to do presbyopic surgery right. You have to have some marketing and sales training for your staff. You have to figure out the economics. You have to figure out how you're going to do touchups. But the option is right there: You can definitely increase your revenue by doing this. The surveys all say that patients want it and are willing to pay for it, and it's also an avenue that's well-supported by our industry, because the vendors also make more money when they sell premium lenses. I think it's the number one option if you need to increase practice revenue.

"I hear lots of excuses from surgeons who aren't doing this," he continues. "Some say the IOLs aren't good enough, but I don't believe that's true—if you hit the target. That means doing a little bit more work with your surgical planning and being able to do touchups, but today's lens implants work very well, and they continue to get better. We've seen incremental improvements with each new lens introduced. I know that some surgeons are concerned that they may not hit the target; they feel more comfortable just doing standard cataract surgery, and that's perfectly OK. But don't blame it on the lenses, which have become quite good.

"Many times we fail to promote the advanced technology of premium IOLs and other procedures that our patients might benefit from because it takes a few minutes longer to explain their benefit and we're running behind schedule," notes Dr. Jarstad. "Sometimes we assume because of the patient's appearance that they wouldn't be interested or have the funds to purchase the premium technology products. I feel this is a mistake.

"In my early days as a cataract surgeon I recall a patient being a little upset and disappointed after her surgery because I hadn't suggested the option of a multifocal or accommodating IOL," he continues. "Many patients will ask family members to assist them financially or use financing when they truly want to be spectacle-independent. I remember a nice, elderly Korean-American lady with cataracts who was on public assistance but asked me about premium IOLs. It turned out that her grateful son was planning to assist her with the fees so she could have her dream of seeing without glasses following cataract surgery. Never judge a person by their appearance!"

Another option is charging to use a femtosecond laser during cataract surgery. "This is an economic opportunity that works well with premium offerings," says Dr. Lindstrom. "The main use for a femtosecond laser in most practices is correcting astigmatism, and it's clear that this isn't being used to its full potential.

"It does require a certain volume of cases to make a femtosecond laser economically viable," he continues. "The typical solo, comprehensive ophthalmologist can't make it viable, although there are mobile services that a solo ophthalmologist can use. Being able to afford a femtosecond laser for use in your practice is another advantage of working in a group."

Dr. Durrie points out another option along the same lines: offering refractive lens exchange, a.k.a. dysfunctional lens replacement. "Patients are willing to pay for lens replacement as a refractive procedure," he notes. "They're impressed to find that they can get rid of near- or farsightedness and astigmatism, improve their near vision and prevent cataract development.

"We need to move away from the term 'clear lens extraction,' because we're not taking out a clear lens," he adds. "The lens has nuclear sclerosis; it's hard and can't change focus. It's a dysfunctional lens."

8 Don't undercharge for services. Dr. Salz points out that some practices undercharge—or don't charge anything—for routine services that aren't reimbursable by insurance. "Medicare and insurance don't pay for a refraction, for example, no matter what the patient's level of vision is," he notes. "That means that patients pay out of pocket for this service, and the practice gets to decide what to charge. Many practices either have a very low fee

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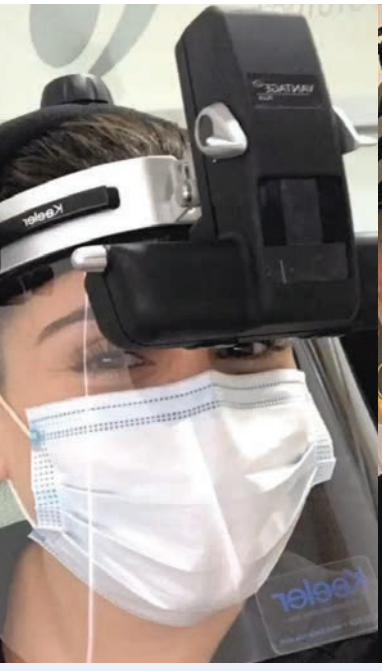

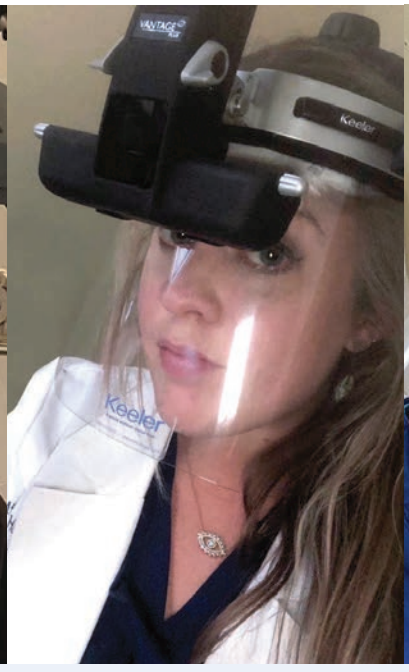

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for a refraction or don't charge anything, and yet the refraction is every bit as important in an eye exam as measuring blood pressure is to an internist doing a complete physical.

"For a long time we were charging a minimal fee of $25 for a refraction," he continues. "Today, if a new patient comes in, we typically bill the insurance for the medical exam and then charge $75 for the refraction, along with $75 for the optional retinal screening exam, which—as already noted—most patients are happy to pay for. That's $150 on top of the medical exam reimbursement. When you consider that you're seeing several new patients every day, that ends up being a significant amount of income."

9 ***Expand your skillset and offerings.*** "American ophthalmologists aren't doing as much minimally invasive glaucoma surgery, or MIGS, as studies suggest we could be doing," notes Dr. Lindstrom. "Also, there are plenty of opportunities to treat dry eye."

Another option is to bring in a surgeon with a specialty such as oculoplastics. Dr. Durrie points out that you need to have the right kind of patient base in order for something like adding oculoplastics to pay off. "If your practice offers private-pay refractive services like refractive cataract surgery, refractive lens exchange and ICLs, then oculoplastics makes a lot of sense," he says. "Premium services tend to attract the type of private-pay patients that will be interested in oculoplastics, and your staff will know how to discuss payment options and explain the value of extra services. But if you take an oculoplastic surgeon and put him into a disease-based practice that doesn't do any private pay, you won't have the right kind of practice style for this to be successful."

Dr. Durrie adds that he recommends bringing in an oculoplastic surgeon, rather than trying to add those skills to your own toolbox. "I think it makes sense for surgeons to stick with what they're already good at," he says. "Remember that we're going to go from four million cataracts today to six million in 10 years. Cataract surgeons are going to be busy enough without trying to expand their skillset."

> **Especially with private-pay options looking more important to the bottom line, getting some business training can make a big difference.**
>
> ***—Daniel S. Durrie, MD***

Dr. Lindstrom says that if you're a solo comprehensive ophthalmologist with a special interest in one area, and you're looking at bringing in another doctor, it's best to bring in someone who has a special interest in one of the other major sectors. "For example, if you were trying to create a maximally effective four-doctor group, it would be ideal to have one doctor's subspecialty interest focused on cornea and refractive; one focused on glaucoma; one focused on plastics; and one focused on medical retina," he says.

"If you don't want to hire a partner, every one of these procedures is something a comprehensive ophthalmologist can be trained to do," he points out. "If you believe one of these could be a good addition to your repertoire, you can start by reading and watching videos; then visit someone who does a lot of those procedures and observe. You can also ask them to mentor you."

Physicians say you might also consider taking a business class. "This is a good time for ophthalmologists to be thinking about how to deal with declining reimbursement and increasing volume," says Dr. Durrie. "Especially with private-pay options now looking more important to the bottom line, getting some business training can make a big difference.

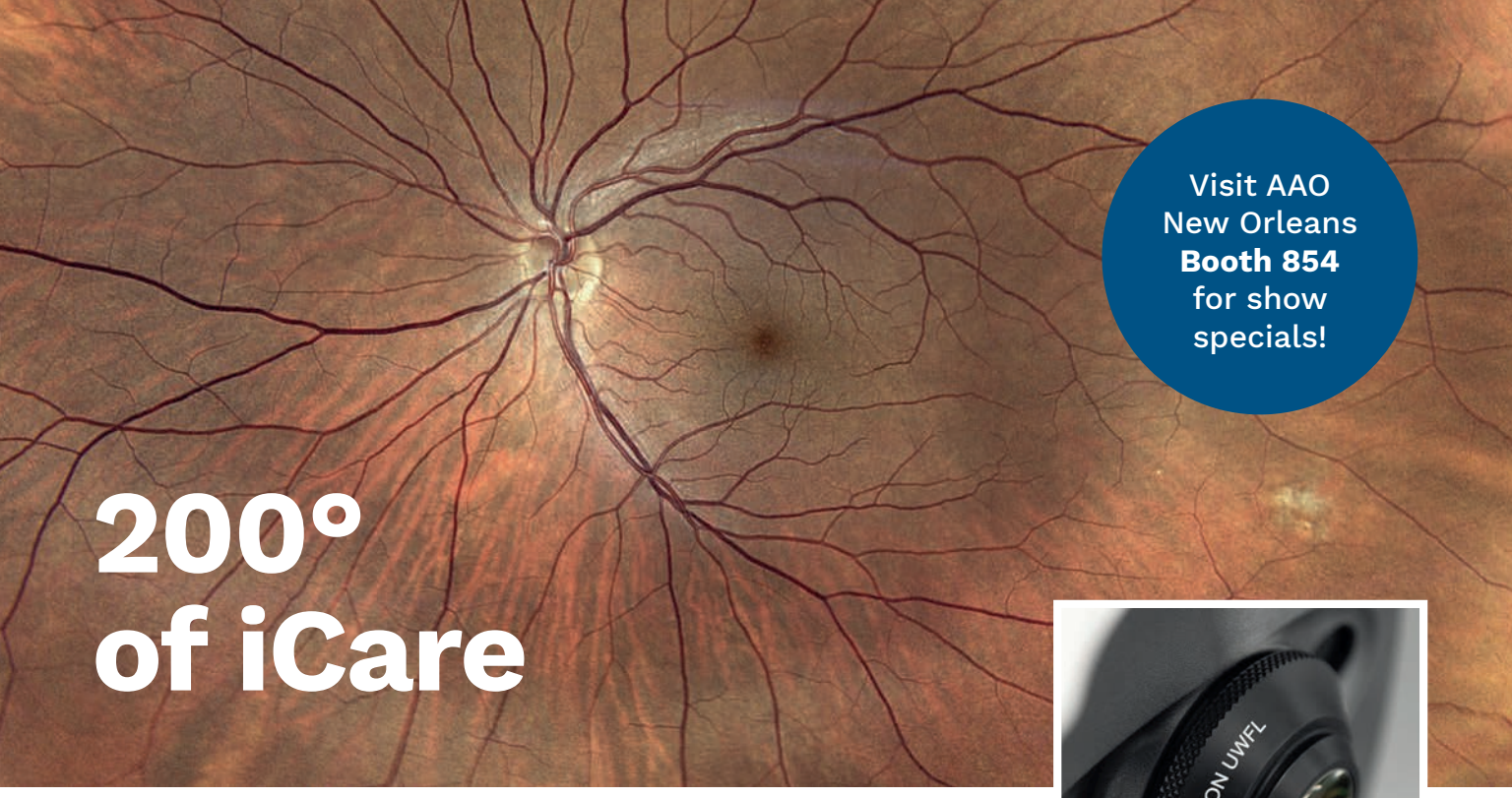
"A few years ago I decided to take the 'Physician CEO' course at Kellogg Business School in Evanston, Illinois," he says. "It's specifically designed for physicians, and it was well worth taking. I learned a whole lot, even though I was successful in business before I took the class. I often found myself thinking, 'Wow—I wish I'd known this 15 years ago.'

"The course is now in its seventh or eighth year, and everyone who takes it says it's terrific," he adds. "It's only open to physicians, with about 35 people in a class. Many doctors say it was life-changing."

10 ***Offer patient-pay alternatives to surgery.*** Another way to generate extra income is to offer medical alternatives to surgery. A new entry into this category is Upneeq (oxymetazoline hydrochloride 0.1%), an FDA-approved first-in-class eyedrop for patients with acquired blepharoptosis (also called "low-lying lids"). Essentially, it allows patients who appear somewhat sleepy to appear more awake and focused.

According to the company, a drop on the eye activates the alpha-adrenergic receptors in Müller's muscle, stimulating contraction, resulting in elevation of the upper eyelids. One of several studies conducted by the company found that use of the drop increased upper eyelid elevation significantly more than vehicle in clinical trials, as measured by marginal reflex distance (the distance from the central pupillary light reflex to the central margin of the upper lid) on day 1 and day 14 of drop usage. Eyelid elevation was evident within five minutes of drop administration. The lid elevation even resulted in a statistically significant improvement in results on the Leicester peripheral field test.

(Continued on p. 48)



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REVISITING VITREOUS LOSS

Be prepared for this cataract surgery complication with expert advice.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

Vitreous loss following a posterior capsule rupture is a stressful complication to encounter during cataract surgery, but keeping up to date on the appropriate approaches and anterior vitrectomy techniques can help prepare you if you end up faced with such a case. Here, surgeons review some of the risk factors and signs of a capsule rupture and discuss the best ways to respond should you lose vitreous.

Risk Factors

Preoperative knowledge is one of the best tools you can arm yourself with before a case, because certain patient factors can make a capsule predisposed to breakage. "It's important to be aware of certain risk factors and to go into the case well aware of the individual patient's ocular anatomy so you're ready for any eventuality," says Rosa Braga-Mele, MD, MEd, FRCSC, a professor of ophthalmology at the University of Toronto. "Risk factors such as posterior polar cataract are often missed because they look similar to posterior subcapsular cataract. Look for the central dot or elicit a history from the patient to see whether they were ever told they had a small cataract when they were younger. A white cataract may also be an unannounced posterior polar cataract that has progressed. When you hydrodissect in these cases, that's often when the lens falls."

Patients who are post-vitrectomy or post-intravitreal injection are also at higher risk for a PCR.[1] Dr. Braga-Mele says that examining the posterior capsule for linear streaks in these patients' eyes can clue you in. "Their capsule may have been brushed by the trocar or needle," she says. "In this case, patient history may include an uneventful procedure followed by rapid development of a cataract. It's best to wait a while before performing cataract surgery to allow the posterior capsule to scar a little more."

Additional risk factors include very short eyes where the anatomy is more compressed, leaving you with reduced working room, and eyes with pseudoexfoliation or zonular issues, where capsular bounce or instability is more likely. "The capsule may be more likely to move and come closer to the phaco tip," Dr. Braga-Mele says. "You could create an iatrogenic tear at that point. These challenging anatomical cases are more likely to have higher complication rates with cataract surgery."

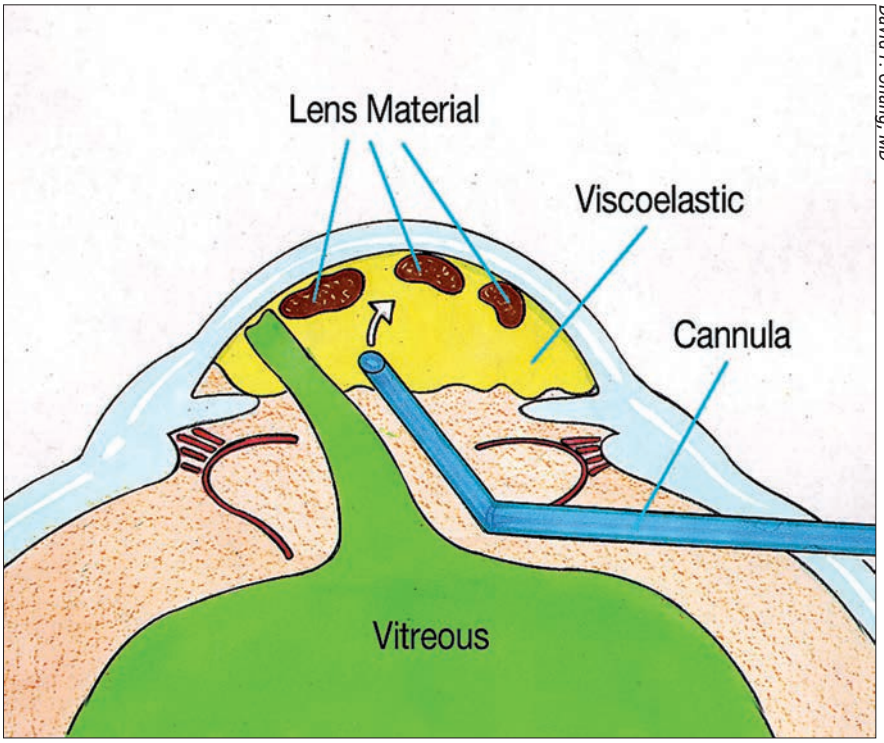
Better Late than Early

Some cases of PCR are unavoidable, but you can take steps to reduce the risk by performing good hydrodissection, says Steve Charles, MD, founder of the Charles Retina Institute in Germantown, Tennessee, and clinical professor of ophthalmology at the University of Tennessee. "Make sure the lens rotates in bag. I use Alcon's Ozil handpiece and perform careful irrigation/aspiration."

Dr. Braga-Mele notes that for cases where the patient may be predisposed to PCR, hydrodissection isn't always the best choice. "I don't hydrodissect in cases where I fear for the integrity of the posterior capsule," she says. "If you know the case is high-risk, use viscoelastic

This article has no commercial sponsorship.

Dr. Charles is a consultant for Alcon. **Dr. Braga-Mele** is a consultant to Alcon, LensGen and Zeiss. **Dr. Chang** reports no relevant financial disclosures.



David F. Chang, MD

Figure 1A. Injecting a dispersive OVD (yellow) maneuvers lens fragments anteriorly and peripherally prior to filling the AC.

to your advantage. I viscodissect, viscodelineate or hydrodelineate to remove the nucleus and then deal with the epinucleus and cortex.

"If you have a case where PCR may be inevitable due to the eye's anatomy, it's better that the PCR occur as late as possible rather than earlier in the procedure when the nucleus can drop," she emphasizes. "With an earlier PCR, you're more likely to have nuclear fragments go into the vitreous." She advises using a dispersive rather than a cohesive viscoelastic in these cases because it creates space more effectively.

In the Hot Seat

Posterior capsule rupture and vitreous loss are rare occurrences in cataract surgeons' careers. The incidence of PCR during phacoemulsification among experienced surgeons ranges from 0.45 to 3.6 percent.[2] Among surgeons recently converting from extracapsular cataract extraction to phacoemulsification, the rates are reported to be 4.8 to 11 percent.[3] Dr. Braga-Mele says that the comments she hears most often from experienced and high-volume cataract surgeons are, "I don't remember what my settings should be," or "I don't know how to do this because I haven't done one in about five thousand cases."

"Refresher articles and courses at the Academy and ASCRS are good for us to do every once in a while to keep up to date on what we should be doing if something should happen," Dr. Braga-Mele says. "If you perform a good vitrectomy, clean-up and lens implantation, your patient can have an outcome as if no complication occurred."

If you encounter a sudden rupture, here are a few things to keep in mind:

• ***First, recognize that a posterior capsule rupture has occurred.*** Surgeons note that residents in particular sometimes fail to notice a posterior capsule rupture. Missing this event could result in retinal tears and detachments from vitreous traction. "If you see sudden deepening of the anterior chamber or capsule wrinkling, be on your guard," says Dr. Charles. Other signs include pupil snap sign, difficulty rotating a previously mobile nucleus (due to vitreous in the capsular bag), excess sideways tilt of the lens or IOL, moments where the pupillary margin is inconsistent with anterior chamber manipulation, and strands of vitreous in the anterior chamber.

Of course, experience helps. In a study reviewing 14,520 cataract surgeries performed at a single center in Finland spanning eight years, researchers confirmed that practice makes for fewer complications. They identified 144 cases (0.99 percent; mean age 76.9) of posterior capsule rupture and/or loss of capsular bag support.[4] Capsular bag-related complications occurred in 0.36 percent of surgeries performed by senior surgeons and in 7.03 percent of surgeries done by residents. Toward the end of the study, these incidence rates improved for residents (1.32 percent) and remained about the same for senior surgeons (0.32 percent). The gradual decline in complications pointed to increasing surgical experience among both resident and senior surgeons.

Another study from 2013 (n=500 eyes) of resident-performed cases reported that 51 eyes (10.2 percent) developed vitreous loss and 48 eyes (9.6 percent) developed posterior capsule rupture and vitreous loss. Risk factors included diabetes, shallow anterior chamber, absence of supervision, larger capsulorhexis, anterior capsule tear and longer effective phaco time. The researchers concluded that direct attending supervision and careful case selection for the level of cataract surgery residency is necessary for avoiding sight-threatening complications.[5]

• ***Your initial reaction is key.*** It's important not to panic and withdraw your instruments. "If lens material falls into the vitreous cavity, pause first," says Dr. Charles. These fragments will remain supported by the vitreous and won't damage the

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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).

Please see brief summary of the full Prescribing Information on the following page.

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. June 2021. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

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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.

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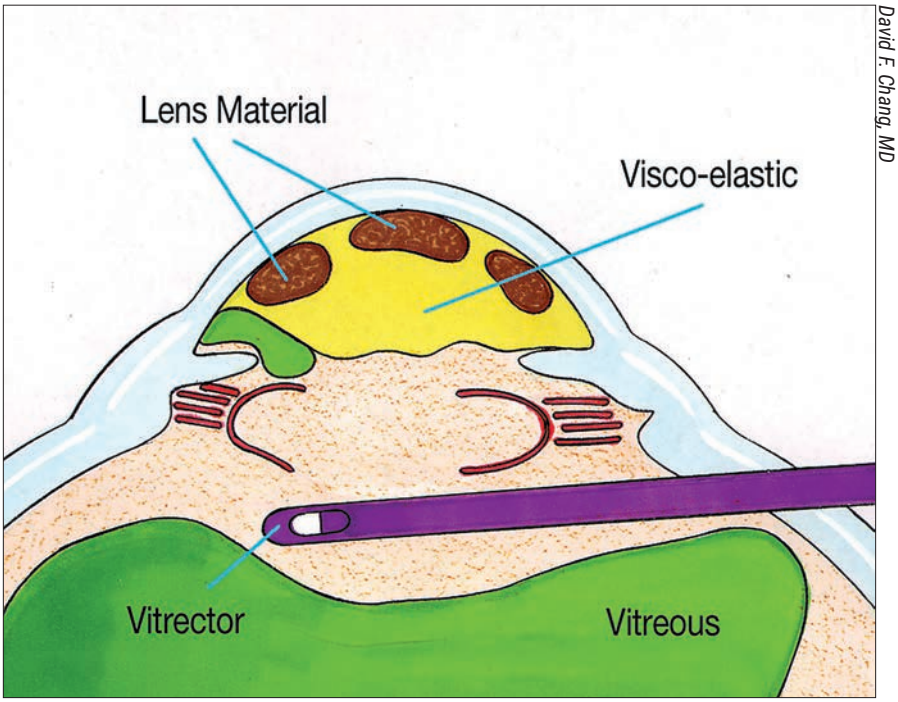


David F. Chang, MD

Figure 1B. The vitrectomy cutter is introduced via a pars plana sclerotomy and transects any forward prolapsing bands of vitreous (green), while remaining behind the pupil. This preserves the dispersive OVD in the AC.

retina, but fishing for them could.

• ***Avoid rupturing the anterior hyaloid face.*** When you recognize that a PCR has occurred, your first objective is to avoid rupturing the anterior hyaloid face, says David F. Chang, MD, of Los Altos, California, and clinical professor of ophthalmology at the University of California San Francisco. "The sudden anterior chamber decompression caused by abruptly withdrawing the phaco tip will cause vitreous to prolapse forward toward and through the phaco incision," he says. "This will expand the posterior capsule opening and set the stage for a cascade of problems."

• ***Assess the extent of the capsule rent.*** "If there's a small rent in the capsule and no vitreous in the anterior segment, perform a posterior continuous capsulorhexis to contain the rent and prevent it from extending," says Dr. Braga-Mele. "If the rent is larger, then the key is to remove all of the nuclear fragments before you start to lose vitreous."

• ***Use a generous amount of OVD.*** If you've already lost vitreous, Dr. Braga-Mele says to push the vitreous back with dispersive viscoelastic. "I then pull any nuclear fragments into the anterior segment over the iris, using the iris as the scaffold to hold the nuclear segment," she explains. "You might even put in a Sheet's glide to partition the vitreous away from the anterior segment and hold the vitreous and the posterior capsule tear back. If there's no vitreous in the anterior segment, I use a dispersive viscoelastic as my second instrument so I can keep pushing vitreous back as I remove the nuclear segment."

• ***Avoid cellulose sponges and impaling the residual nucleus with the phaco tip.*** "Mopping externally prolapsed vitreous with a Weck-Cel sponge causes traction on the vitreous base," Dr. Chang says. "Additionally, you shouldn't attempt to impale the residual nucleus with the phaco tip. This risks vitreous incarceration and a giant retinal tear. Because residual nuclear fragments are supported by the vitreous, they'll likely descend posteriorly as an anterior vitrectomy is performed. Injecting OVD via a side port paracentesis prior to withdrawing the phaco or IA tip is key to preventing forward vitreous prolapse and rupture of the hyaloid face."

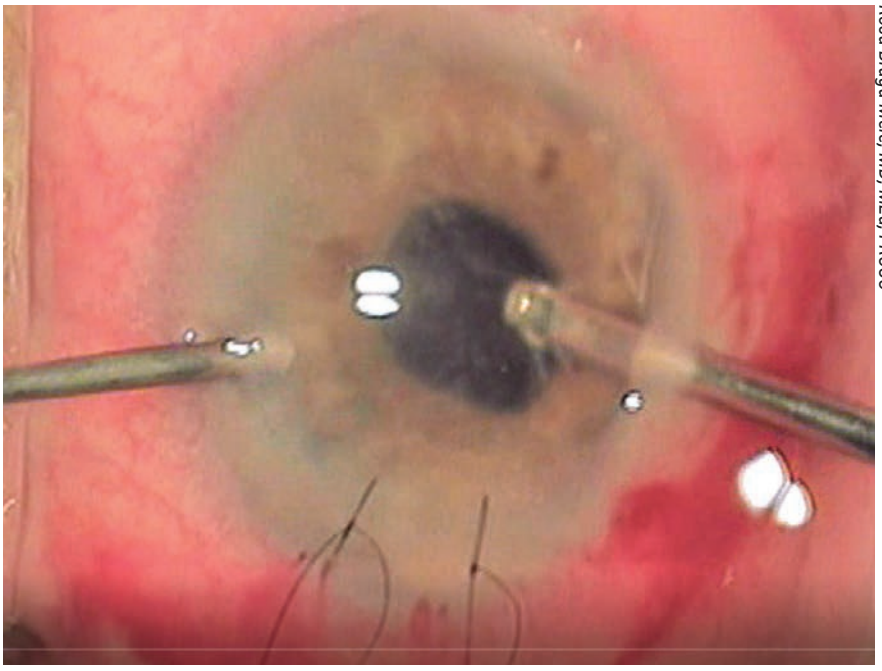
Performing Anterior Vitrectomy

If there's vitreous in the anterior chamber, it's time to perform an anterior vitrectomy. But before beginning, it's important to ensure the patient's pupil dilates and that the cornea is reasonably clear (i.e., no extensive miosis or keratopathy). Experts say your goals for this procedure should be to minimize both intraoperative and postoperative vitreoretinal traction, as well as any mechanical trauma to the iris, which is a major cause of CME.

"Once vitreous prolapse has been identified, the foremost objective is to avoid aspirating vitreous with the phaco or IA tip," says Dr. Chang. "Never attempt to spear or aspirate residual nucleus with the phaco tip, despite the temptation to prevent its descent. Once the posterior capsule is open, it's the vitreous that keeps nuclear material from descending onto the retina."

He advocates a sequence of steps that he calls the "Viscoelastic Trap." To perform it, first inject triamcinolone into the AC to stain any prolapsing vitreous. Next, use a dispersive OVD to maneuver lens material anteriorly and peripherally above the iris (*Figure 1A*). Then, completely fill the AC with dispersive OVD. "I then perform a biaxial anterior vitrectomy through a pars plana sclerotomy, with a self-retaining infusion cannula placed through a limbal paracentesis (*Figure 1B*).

"The goal is to keep the vitrectomy tip behind the pupil while excising the central anterior vitreous and transecting any forward-prolapsing vitreous bands," he continues. "In this way, the dispersive OVD filling the AC is not removed; it remains in place, continuing to trap all the



Rosa Braga-Mele, MD, MEd, FRCSC

Figure 2. Intraoperative image showing a bimanual anterior vitrectomy with the main incision sutured and the vitreous stained with triamcinolone peripherally prior to filling the AC.

loose lens material. Once the bands of prolapsed vitreous have been cut, it's safe to remove the remaining OVD-suspended lens material. This might be with biaxial IA for epinucleus and cortex, or with a phaco tip for nuclear fragments. For the latter, place a three-piece IOL in the sulcus or into the AC to serve as an IOL scaffold. Popularized by Amar Agarwal, the IOL optic prevents nuclear fragments from descending while simultaneously blocking vitreous from being aspirated. Any loose bits of vitreous in the AC that have been transected from their attachment to the vitreous base can and will be safely aspirated in the process."

Dr. Braga-Mele says that one of the keys to removing vitreous is to perform the anterior vitrectomy bimanually, splitting irrigation and aspiration by creating two new wounds. "You have to go to a bimanual vitrectomy system at this point and abandon your main wound if you have vitreous," she says. "Clean up the vitreous and push it back. When you're cutting or removing vitreous, it's important to do irrigation, cut then aspiration, as opposed to when you phaco, where you do irrigation, aspiration, then cut. You want to be sure you're never pulling on vitreous, but always cutting it to avoid retinal traction.

"The reason you abandon your main wound is that vitreous will go to the area of least resistance, and the main wound is that place," she says. "If you go through the main wound you'll just keep expressing more vitreous."

Dr. Charles adds that you should never withdraw the vitreous cutter while vacuum is applied. "You can cause retinal breaks if the cutter is withdrawn while vacuum is applied," he says. "Excessive flow rates or less-than-maximum cutting rates can also cause traction. For your parameters, you should use the highest available cutting rate and very low infusion pressure/bottle height, as well as the lowest effective flow rate." The cut rate should be at least 1,200 cpm or more.

Another key to the anterior vitrectomy is clearing away all of the vitreous before continuing to remove any nuclear fragments. One way, considered old-fashioned and no longer advised because it results in retinal traction, is the use of cellulose sponges to test for vitreous. "For this method, typically, if the pupil is round and there aren't any strands coming to the Weck-Cel site, then you've removed enough vitreous to keep moving forward," says Dr. Braga-Mele.

"The other, preferred way to check for residual vitreous is by using intracameral triamcinolone," she continues. "It's available without preservatives from certain companies. Triamcinolone will stain the surface of the vitreous, but you must keep reinserting it because it only stains the surface. Proceed and cut away what you see and then reinsert a bit more to see if you got it all. Use Miochol-E (acetylcholine chloride intraocular solution; Bausch + Lomb) and Miostat (carbachol 0.01% intraocular solution; Alcon) to shrink the pupil. If the pupil comes down into a really nice, tight 2- to 3-mm pupil, then you know you've probably removed most of the vitreous, because vitreous will cause pupil peaking."

If you're not careful, you can vitrectomize the capsule and wind up with nowhere to put the IOL, she adds. "Also, removing too much vitreous can cause the eye to become over-decompressed or cause choroidal edema."

Limbus or Pars Plana

Should anterior segment surgeons perform a pars plana vitrectomy during cases such as these? This question has generated a lot of debate. "Pars plana vitrectomy is better if the surgeon is trained," says Dr. Charles. "It's better for the corneal endothelium and the iris. Always infuse through a sideport, with the cutter through the pars plana or second sideport, bimanually."

However, many anterior segment surgeons aren't comfortable or expe-

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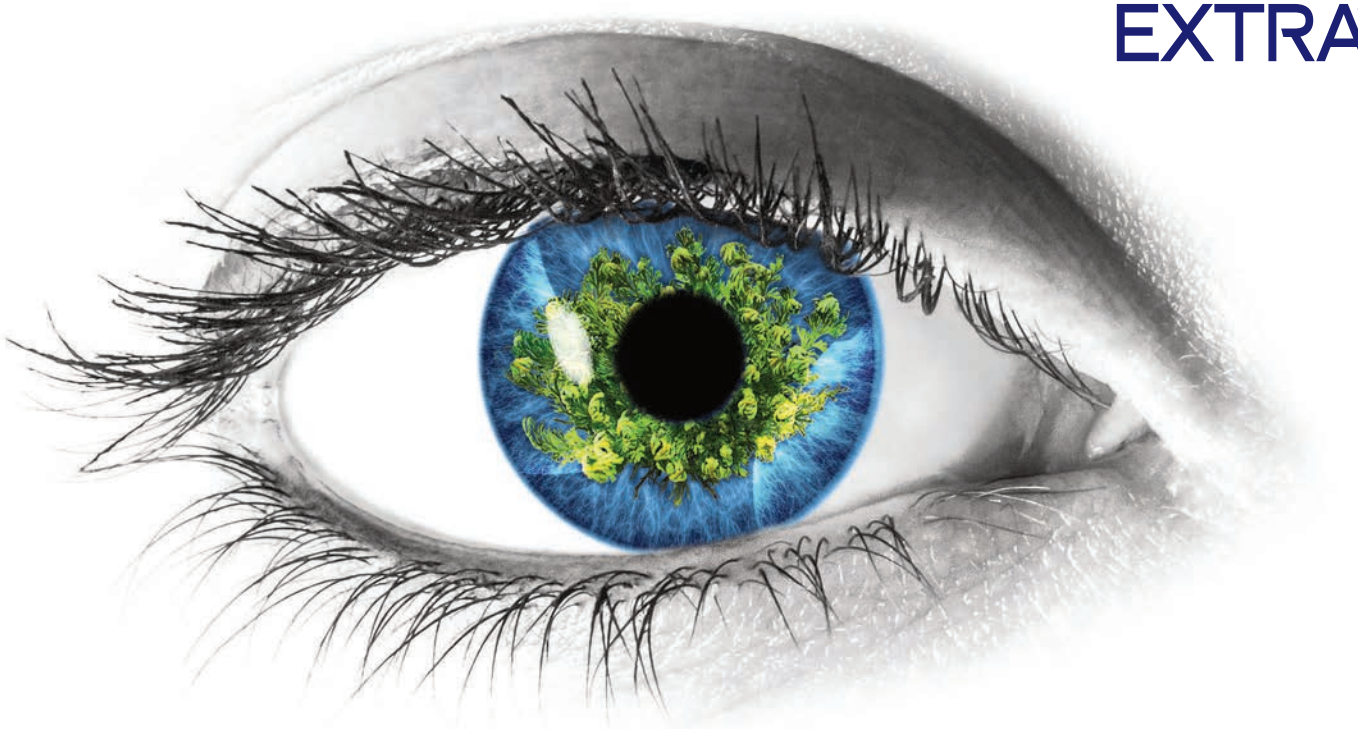

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Reference: 1. Jones L, Downie L, Korb D, et al. TFOS Dews II Management and Therapy Report. The Ocular Surface Jul 2017; 575-628.

rienced with performing an anterior vitrectomy through a pars plana sclerotomy, Dr. Chang points out. "Performing a biaxial limbal vitrectomy may be the more comfortable and familiar alternative," he says. "Any posteriorly retained lens material can be subsequently removed by a vitreoretinal surgeon, with an excellent prognosis. Regardless of the vitrectomy approach, repeated triamcinolone injections can confirm complete excision of any prolapsed vitreous."

Dr. Braga-Mele agrees, saying that cataract surgeon comfort should be the determining factor. "The main thing is to split irrigation and aspiration, whether you're performing an anterior limbal or modified posterior vitrectomy," she says. "If you're doing a posterior vitrectomy, you must understand the anatomy of choroidal vessels and not go into the three or nine o'clock positions, because you could cause choroidal hemorrhage. Go only 3.5 mm posterior from the limbus to avoid causing occult tears.

"I still use my irrigation anteriorly through the limbus, even when I use a vitrector posteriorly," she continues. "You don't need to do a conjunctival cut-down when you do a posterior vitrectomy, but you should use a clean MVR or sideport blade to make the incision so you don't traumatize the retinal anatomy. Lastly, you need to cut on the way out and make sure no vitreous comes back out through the posterior vitrectomy incision."

Lens Implant Options

Dr. Chang says the remaining capsular anatomy will determine the IOL options available to you. "With a large posterior capsular rent but an intact capsulorhexis, a three-piece IOL in the sulcus with optic-CCC capture is an excellent strategy," he says. "If there's a wraparound anterior capsular tear that extends across the posterior capsule, I would consider a three-piece IOL in the sulcus without optic-CCC capture.

"Options for implanting a single-piece acrylic refractive IOL (e.g., toric or EDOF) might include converting a PC defect into a posterior CCC, or using the anterior CCC for reverse optic capture," he adds. "If there's insufficient capsular support, scleral fixation of an IOL is a consideration. A properly sized and positioned AC IOL is another acceptable option, particularly if the surgeon isn't comfortable with alternative techniques of non-capsular IOL fixation."

> ***Regardless of the vitrectomy approach [pars plana or limbus], repeated triamcinolone injections can confirm complete excision of any prolapsed vitreous.***
>
> ***—David F. Chang, MD***

Dr. Braga-Mele notes that if she performs a posterior vitrectomy, she pairs herself with a retinal surgeon. "This way, the retinal specialist can perform a good retinal exam for me," she says. "You can induce a giant retinal tear if you're not careful." She has patients see a retinal specialist two to six weeks after surgery. ◀

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DEFYING ECONOMIC GRAVITY

(Continued from p. 38)

The company says the drug's safety is comparable to placebo. The most common adverse reactions are punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation and headache, seen in 1 to 5 percent of patients; 2.2 percent of patients in the trials discontinued treatment due to an adverse event.

Kenneth J. Rosenthal, MD, FACS, an associate professor of ophthalmology at the John A Moran Eye Center, University of Utah, and surgeon director at Fifth Avenue Eye Care and Surgery/Rosenthal Eye Surgery in New York City, says that he and several of his colleagues are offering Upneeq drops to patients with ptosis; he's prescribed it for 30 or 40 patients so far. He sees it as trying medical therapy before resorting to surgery. "It stimulates the Müller's muscle in the upper lid, raising it for about six hours," he explains. "It keeps many patients with mild degrees of ptosis from needing to have surgery. We've used it with some success." He notes that the company has announced the rollout of a program allowing doctors to sell the product from their practices. (He plans to participate.)

"It's especially good for patients who aren't good surgical candidates, either because their ptosis is mild, or because they have medical problems that preclude them from having surgery," he adds. "I'm not aware of any failures, except for one patient whose ptosis was too severe. This allows us to say, 'Well, we tried medical therapy first before going to the OR.' "

You can find out more about Upneeq at ecp.upneeq.com/what-upneeq-offers-your-patients/. ◀

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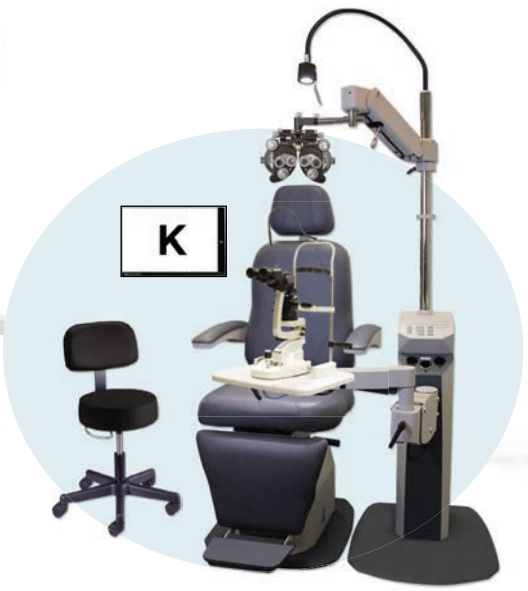

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HOW TO HANDLE NORMAL-TENSION GLAUCOMA

Glaucoma experts consider what we know about this condition, patient management strategies and unanswered questions fueling research efforts to redefine it.

LINDA GROSS
SENIOR EDITOR

While glaucoma is commonly associated with elevated intraocular pressure, a subset of primary open-angle glaucoma can be classified as normal-tension glaucoma, an optic neuropathy known to wreak the same ocular havoc as POAG. "Normal" refers to IOP measurements of 21 mmHg or lower. Terms like "low-tension" and "low-pressure" glaucoma have fallen out of favor because "low" is a relative term for this subset of patients, and current treatment strategy remains focused on lowering IOP. But the complexities in this subpopulation lay the groundwork for theories and research, which could have larger implications for future disease classification and treatment.

Here, experts discuss the current approaches to treatment and weigh in on alternative perspectives to simply characterizing patients as having normal tension glaucoma within a subset of POAG.

> **"The diagnosis of NTG is only reached after excluding other forms of optic neuropathy, such as ischemic, traumatic, toxic, inflammatory, infectious, congenital or compressive conditions."**
>
> ***— Razeghinejad Mohammadreza, MD***

Unique Characteristics of NTG

Despite lower IOP and open anterior chamber angles seen on gonioscopy, NTG patients aren't spared tell-tale optic nerve head damage, progressive retinal nerve fiber layer thinning and visual field defects.1 But there are nuances. "NTG patients tend to have more focal notching in the rim, and they're more likely to develop disc hemorrhages or flame-shaped hemorrhages across the rim of the disc," explains Leonard Seibold, MD, an associate professor of ophthalmology at the University of Colorado School of Medicine. "These often happen adjacent to preexisting notches in the rim. They also tend to have more paracentral scotomas on their visual field testing compared to high-pressure glaucomas, which typically affect peripheral vision early and central vision later."

All Things Considered

"The diagnosis of normal-tension glaucoma is only reached after excluding other forms of optic neuropathy, such as ischemic, traumatic, toxic, inflammatory, infectious, congenital or compressive conditions," said Razeghinejad Mohammadreza, MD, director of the Glaucoma Fellowship Program at Wills Eye Hospital in Philadelphia. "A neuroimaging evaluation is highly suggested in atypical cases, such as a younger patient with a decrease in visual acuity, impaired color vision, pallor of the neuroretinal rim, highly asymmetric cupping and VF defects respecting the vertical meridian."

This article has no commercial sponsorship.

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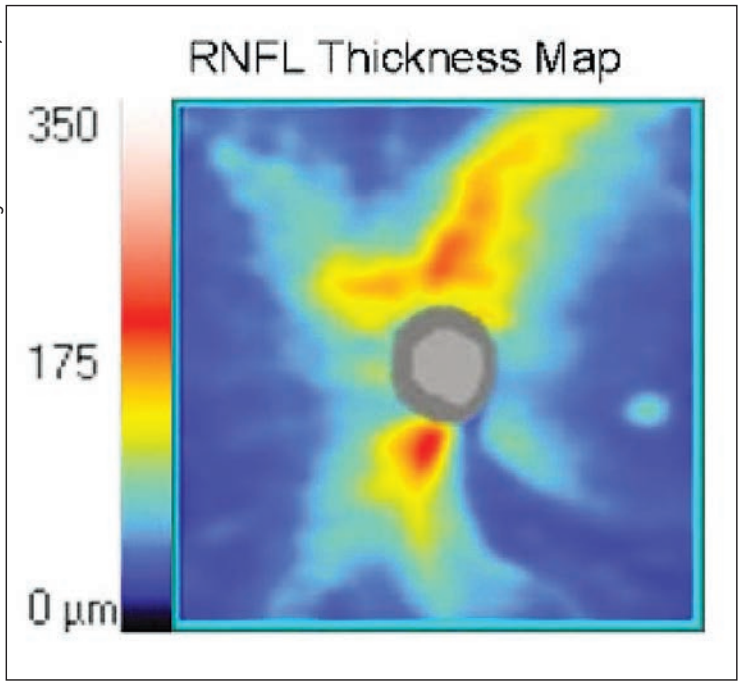


All Images: Leonard Seibold, MD

Focal retinal nerve fiber layer thinning is seen in the inferotemporal location in an eye with normal-tension glaucoma.

"It's a diagnosis of exclusion," agrees Peter A. Netland, MD, PhD, Vernah Scott Moyston professor and chair of ophthalmology at the University of Virginia School of Medicine in Charlottesville. He says that if the eyes are markedly asymmetrical and one eye is highly abnormal, for example, if it has a lot of cupping and optic nerve atrophy or other findings such as pallor of the neuroretinal rim or loss of color vision, and the patient is under [the age of] 60, then he considers a differential diagnosis. "That's not to say a 40-year-old can't have NTG," says Dr. Netland, "but anything that's not in the typical findings would raise my suspicion that it might be something else."

NTG Masqueraders

Identifying NTG masqueraders is a challenge. "It could be some type of glaucoma the person may have had, which is now resolved or in remission," or it could be a nonglaucomatous condition, notes Dr. Netland. "Classic examples include vascular diseases, [exposure to] certain toxins such as methanol, syphilis or congenital anomalies. There are many possibilities. We're constantly looking for other diagnoses to make sure we can exclude them first."

How Low Can You Go?

For the most part, "we treat NTG the same as primary open-angle glaucoma," explains Dr. Seibold. "We're just starting from a normal pressure and getting to an even lower pressure." He says this approach has become a standard since the 1998 Collaborative Normal Tension Glaucoma Treatment Study.2 "It proved that a further reduction in pressure does in fact alter the course of the disease, so we can stabilize a lot of disease by a 30-percent reduction in pressure," Dr. Seibold says. "It's a good guideline for most patients to lower pressure by at least 20 percent, but each eye is different. Some need a pressure of 12 mmHg, some need a pressure of 10 mmHg, and some need a pressure of 8 mmHg."

Dr. Mohammadreza says that, as with POAG, "The treatment algorithm is the same and can include selective laser trabeculoplasty, medication and MIGS or filtering surgeries, based on the severity of the glaucoma."

Medications and NTG

Prostaglandin analogs are the most widely prescribed glaucoma medications, but newer therapeutic classes for NTG nonresponders have broadened physicians' options.

"Sometimes our treatment approach is a little nuanced, particularly for medications," says Dr. Seibold. "Using rho kinase inhibitors can potentially lower episcleral venous pressure and may help us to get even lower pressures, playing more of a role in normal-tension glaucoma."

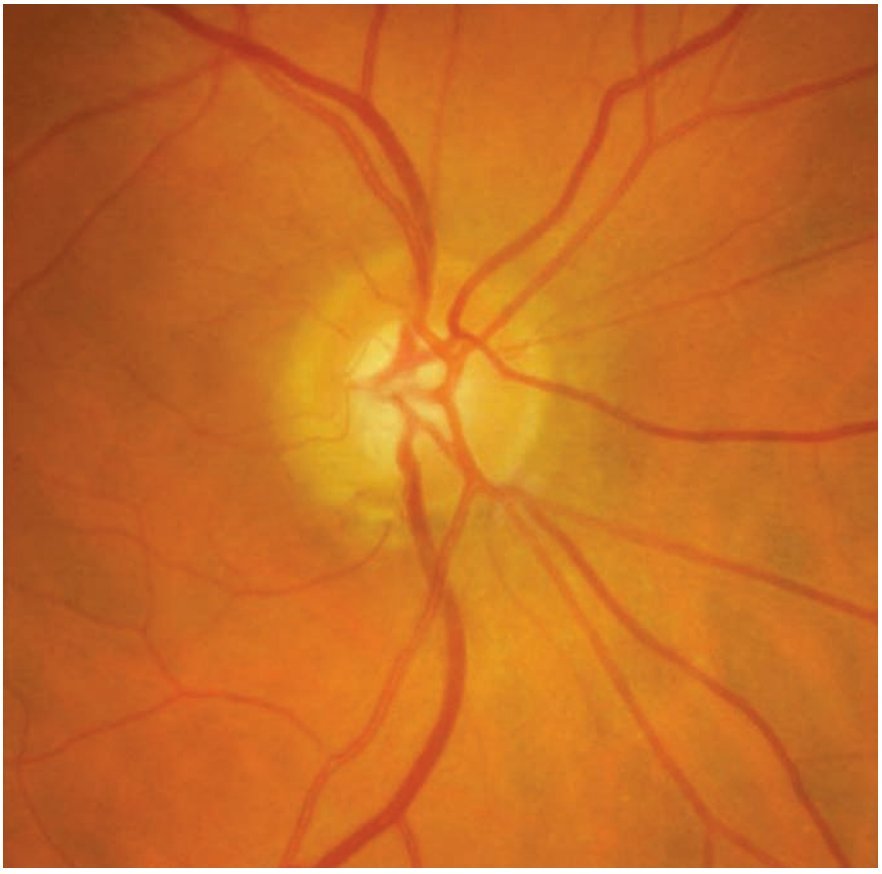
Dr. Netland agrees the newer class of rho kinase inhibitors may have a role in NTG, noting that although they haven't been studied in this population, their ability to increase the drainage of intraocular fluid could prove beneficial in lowering IOP for these patients.

He speculates that interest could resurge in drugs with neuroprotective or neurovascular effects that are used for lowering IOP, recalling the Low-Pressure Glaucoma Study Group from 2011. In that study, researchers compared brimonidine tartrate 0.2% to the beta-adrenergic antagonist timolol maleate 0.5%. The primary endpoint was preservation of visual function in low-pressure glaucoma, and statistically fewer brimonidine-treated patients (n=9; 9.1 percent) had visual field progression by pointwise linear regression than timolol-treated patients (n=31; 39.2 percent, log-rank 12.4, p=0.001). Mean IOP was similar in both groups.3 "I think it's an interesting study and it has been influential," Dr. Netland noted.

He says that carbonic anhydrase inhibitors "have known beneficial effects on retinal circulation," but a magic bullet for NTG patients remains elusive.

Lasers and Surgery

"Selective laser trabeculoplasty has been shown in NTG patients to reduce fluctuation of IOP, avoiding peaks in patients who are progressing," notes Dr. Netland. "It's used to keep average pressures in the mid-



Inferior optic disc rim notching in an eye with normal-tension glaucoma.

to low-teens. You may not see much effect on the average pressure you measure in the clinic, but the idea is that you might be cutting off undetected peaks. That's been found to be the case in trials.

"Obviously all of us, including myself, are moving on to MIGS," Dr. Netland continues, "particularly with transscleral devices and sometimes with adjunctive therapy. MIGS can achieve pressures that are close to or equivalent to SLT, so I think we're shifting a bit more in that direction."

However, Dr. Netland cautions that "some of the MIGS aren't as effective in lowering IOP and may not achieve the goals we're trying to target."

Dr. Seibold agrees that MIGS has a role in NTG treatment, but acknowledges limitations. "A lot of the angle procedures like Kahook Dual Blade (New World Medical), iStent (Glaukos) and Hydrus (Ivantis) are very good at lowering pressure from the 20s and 30s back to a normal range, but when you're starting in the mid-teens, they don't offer a lot in the way of lowering IOP further, so we often have to go to a filtering surgery like a trabeculectomy to get those really low pressures under 12 mmHg," he explains. "That's why MIGS has less of a role in NTG."

> **"The median range of [NTG's] prevalence that's been reported in the U.S. is about 20 to 30 percent of glaucoma patients."**
>
> ***— Peter A. Netland, MD***

Patient Characteristics

Refining treatments to target a subgroup of patients is even more of a challenge when prevalence data comes into question. One paper cites a worldwide NTG prevalence range between 30 and 90 percent.[4]

And, while NTG is higher in Asian populations, "The median range of prevalence that's been reported in the U.S. is about 20 to 30 percent of glaucoma patients," notes Dr. Netland. "It's certainly not rare. It's not an uncommon condition."

Some speculate that low daytime IOP measurements could misclassify NTG. "Some of these patients may have POAG with significant IOP fluctuation," notes Dr. Mohammadreza. "Peak IOPs may be happening during out-of-office hours. Some of the NTG patients could be labeled as POAG after having a diurnal curve. A modified diurnal curve, which involves checking the IOP during office hours every one to two hours, certainly misses any IOP spikes happening at night, in the early evening, and in the morning." Dr. Mohammadreza says that the iCare home tonometer could be useful for assessing diurnal variations.

Dr. Seibold agrees. "Studies show that up to two-thirds of patients will have their peak IOP outside of office hours," he says. Thus, despite varying morning and afternoon visits to document IOP spikes, he says, "We may still miss it. That's where home tonometry can now play a role, because we can have patients use a home tonometry device and measure those pressures after-hours: early morning; evening; late at night."

Thus, "while NTG in the U.S. makes up about one-third to maybe as many as half of the glaucoma cases we see, it may be actually less than that, and it's just misclassified because we're missing the high pressures," Dr. Seibold speculates.

Based on home tonometer readings, New York's Icahn School of Medicine professor Louis R. Pasquale, MD, says, "We're finding that pressures outside of the office are much higher than they are in the office." This may explain why

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Warnings and Precautions:

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

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

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

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

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

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

Adverse Reactions:

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

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

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

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

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ADVERSE REACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

NONCLINICAL TOXICOLOGY

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

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patients are progressing, but it also opens a can of worms for him in terms of NTG as a glaucoma category. Dr. Pasquale speculates that if more NTG patients checked IOP at off hours, they would see pressures higher than 21 mmHg. "Generally speaking, stratifying patients with glaucoma based on IOP has not been that informative," he says. *(See sidebar, "Turning Normal Tension Glaucoma on its Head," right.)*

Guilt by Association

Patients often want to know what causes their condition. Glaucoma specialists have few answers for those with NTG. "The etiology is unknown," notes Dr. Netland. "A lot of things might influence NTG." Associations include migraine and Raynaud's syndrome, the latter of which suggests what Dr. Netland calls "some sort of vascular dysregulation."

"Vascular dysregulation as a factor in the development of glaucoma seems to play a major role in NTG compared with POAG," agrees Dr. Mohammadreza.

In addition, Dr. Netland says, "Various other problems have been associated with NTG, such as hypertension, hypotension, ocular perfusion pressure abnormalities, and there are some intriguing findings about CSF pressure."

Another theory holds that NTG eyes may have a demographically different tolerance and/or genetic susceptibility to an IOP within the normal limit, according to Dr. Mohammadreza. "In addition, a large percentage of older NTG patients suffer from Alzheimer's disease," he adds.

The Alzheimer's link has piqued physicians' interest in the vasoprotective and neuroprotective treatment strategies, to which Dr. Netland referred earlier. "But, as clinicians, we have to go with what we know is effective, and IOP already does have this role," says Dr. Mohammadreza.

Myopia has also been linked to NTG, but as they say, sometimes a cigar is just a cigar. Robert T. Chang, MD, assistant professor of ophthalmology at Stanford's Byers Eye Institute, explains that, "myopia can be associated with elongation of the eye and resultant tilting and torsion of the optic nerve head, causing visual field defects that may resemble glaucomatous damage, but are simply the result of myopia, and not glaucoma," as he noted in the May 2017 issue of Review.

The Hypertension Connecton

Pinpointing associations with NTG may not change current treatment interventions; however, the hypertension/hypotension correlation to NTG is enough to compel some glaucoma specialists to take an active interest in a patient's hypertensive medication regimen. "I always bring that topic up with my NTG patients, particularly those who are progressing despite a low IOP," says Dr. Seibold. "If they seem to be at their target IOP, I'll ask if they have systemic hypertension. Sometimes they're overtreated to the point where their systolic blood pressure dips into the 90s. That can be detrimental, because now you're lowering the ocular perfusion pressure," he notes.

Just as the home use of tonometers may uncover off-hour IOP spikes, the use of Holter monitors has uncovered blood pressure readings a physician wouldn't see in the office. "Holter monitoring can be a really nice thing because you get a 24-hour record of what's happening with the patient's cardiovascular

TURNING NORMAL-TENSION GLAUCOMA ON ITS HEAD

"There are some people who feel that 'normal-tension' glaucoma should be excised from our vernacular," says Louis R. Pasquale, MD, professor of ophthalmology, Icahn School of Medicine at Mount Sinai in New York. He rarely uses the term in patient charts and says using 21 mmHg as a cutoff to classify NTG is akin to "drawing a line in the sand." Dr. Pasquale rattles off population studies like the Barbados Eye Study, which found glaucomatous damage occurring between 18 and 24 mmHg, and a study in Norway describing glaucomatous damage within so-called "normal" pressures.[1,2] In addition, he says that people like to say NTG is more common in Asia, and it is, but that population has lower BMI and lower rates of hypertension. He theorizes that if the U.S. population mirrored these anthropometric measures, "we'd see the same thing."

But NTG is more than one thing. Dr. Pasquale likes to say that he has taken the "P" out of POAG; grouping glaucoma by African-American race, estrogen deficiency, mitochondrial stress and endoplasmic reticulum stress, for example. "But I found that for any one patient, it's hard to define those mechanisms, and patients probably have multiple mechanisms, so now I'm saying let's just let the disease define itself," he says. "Let the visual field be a read-out of the pattern of loss." With NIH funding, he says that he and his colleagues are looking at visual defects and using artificial intelligence to turn them into a linear equation that quantifies the different regional patterns of loss.

With 14 different patterns now identified, the next step is mapping these to the 120 genes they've identified as being associated with glaucoma. "Using two hospital-based repositories, we give everybody a genetic risk score," Dr. Pasquale explains. The research also has an environmental component, which could further inform risk factors. By defining glaucoma in terms of disease process and establishing genetic links to visual defects like para-central loss, superior defects and inferior defects, Dr. Pasquale believes this establishes a more informed epidemiological framework. "We're hopeful that we'll be able to stratify more people, not by IOP, but by genetic risk score," he says. The findings may do more than turn NTG on its head; they could reframe how POAG is classified, paving the way for targeted therapies. "The semantics issue is important," says Dr. Pasquale. "We're evolving from 'low-tension' to 'normal-tension' to everything else being POAG, so let's take the 'P' out of it and figure it all out so we can have a precision-based medicine approach to the disease."

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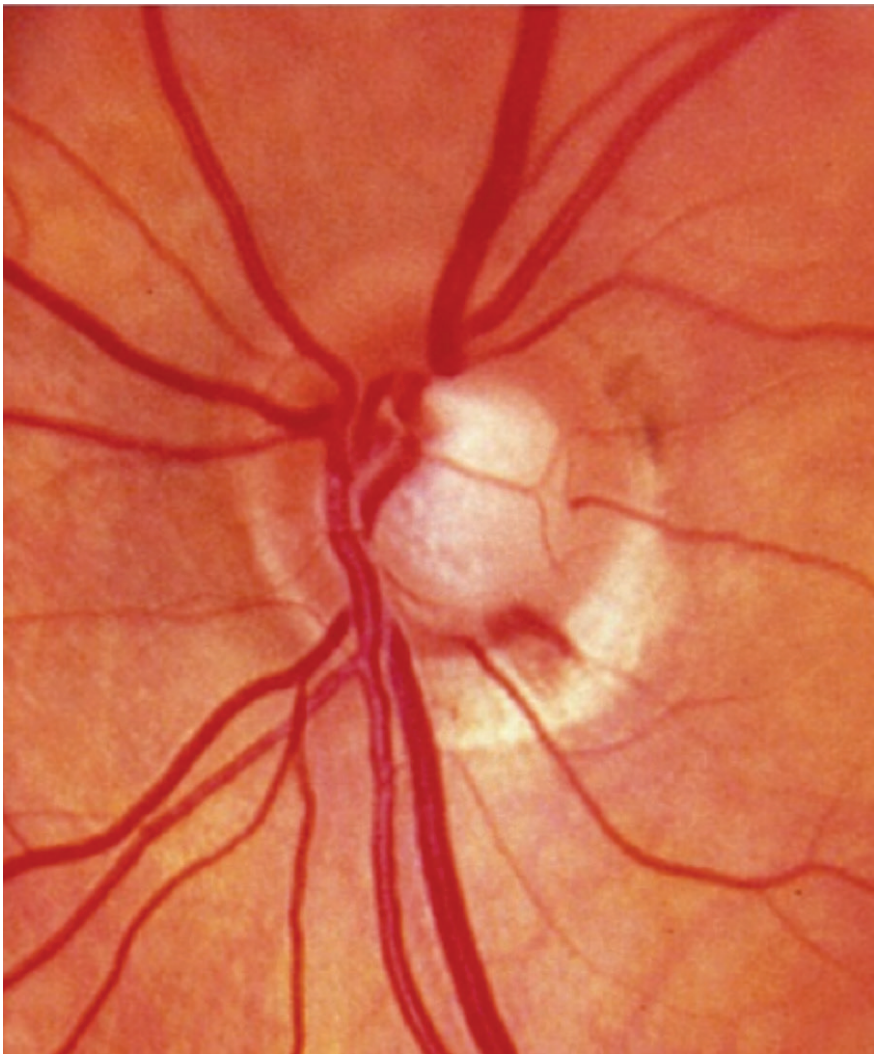
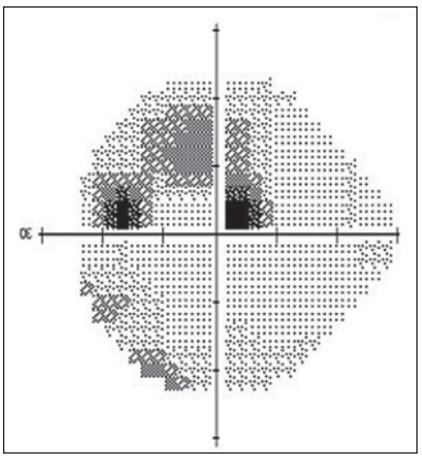


Optic disc hemorrhage in an eye with normal-tension glaucoma.



Paracentral visual field loss in an eye with normal-tension glaucoma.

parameters, and that can lead to tremendously helpful insights in some patients," says Dr. Netland.

It may come down to a log of blood pressure measurements and a conversation with the patient's primary care doctor, asking: "Can we [adjust blood pressure medications] to the benefit of higher ocular perfusion pressure?" Dr. Seibold suggests.

Next Steps in NTG

"Overall, NTG has a fairly intractable clinical course," says Dr. Netland. "But you can still reduce the rate of progression significantly, so that's a very positive thing for patients. They're not likely to go blind on their treatment, so there are many positives here." That's not to say that he doesn't want to push the envelope for more effective treatments.

> **"We give a one-size-fits-all answer and say, 'Most people with glaucoma, they're going to do OK.' But that's disingenuous when we can say out of the other side of our mouth: 'It's the leading cause of blindness.'"**
>
> ***— Louis R. Pasquale, MD***

"Dropping the pressure by 30 percent doesn't stop NTG," Dr. Pasquale says of current interventions. "It still progresses. We need to explore alternative paradigms of treatment." He says that the need for more aggressive treatments is evident for some patients, and he and his colleagues are working toward figuring out who those patients are. Today, he says, "We give a one-size-fits-all answer and say, 'Most people with glaucoma, they're going to do OK.' But that's disingenuous when we can say out of the other side of our mouth: 'It's the leading cause of blindness.' Clearly not everybody is doing OK. We really need to be able to do a better job of forecasting so we can figure out who to be more aggressive with in using our current tools—until we get better tools." ◀

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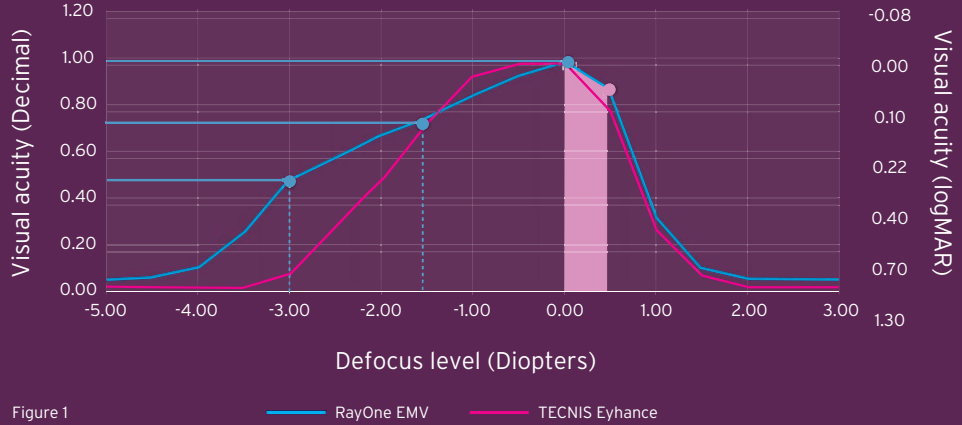

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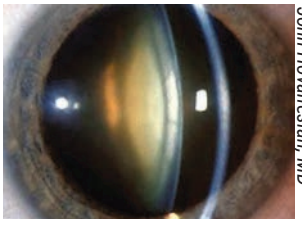
MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Phakic intraocular lenses are sort of an "option of last resort" for patients who really want refractive surgery but don't qualify for LASIK or PRK due to high refractive errors or corneas that are too thin. Though they expanded the range of refractive surgery when they arrived in the United States years ago, they didn't catch on in the way some hoped. Even so, phakic lenses remain a viable option for certain patients, and surgeon interest may increase if and when the latest version of the Visian ICL is approved.

If you've got patients who might qualify for one of these lenses and want a primer on implantation, or you've already implanted a couple and want to hear how other surgeons approach them, read on.

Phakic IOLs in the United States

Currently, the Visian ICL and Ophtec's Verisyse/Artisan are the only phakic IOLs approved in the United States. "The toric version of the ICL was recently FDA approved and is terrific for patients who have astigmatism," says John Hovanesian, MD, who is in practice in Laguna Hills, California. "These lenses are indicated for myopia or myopia with astigmatism, and they work very well. Some docs feel that the results they achieve with phakic IOLs are better visually than the results they get with LASIK."



John Hovanesian, MD

Proper white-to-white measurement is key for the ICL.

According to Santa Clara, California, surgeon Huck Holz, MD, most surgeons in the United States favor implanting the Visian ICL. "The Verisyse requires a larger incision, the recovery is slower, and outcomes are not as predictable," he says. "We also have to worry over the long term about the patient's endothelial cell counts, so most people have gravitated toward the ICL."

Patient Selection/Education

Ideal candidates for phakic IOL implantation are relatively young patients who have high myopia and are looking for good-quality vision. "This is a reasonable option even for patients with keratoconus, provided that spectacle correction gives them a satisfactory outcome," Dr. Hovanesian says. "One of the nice things about an ICL is that, if patients see well with spectacles, then you know that they'll see well with an ICL. Additionally, if patients are in their 50s, they are high myopes, and they are not ready for cataract surgery, an ICL is still a reasonable option."

Minneapolis surgeon David Hardten notes that patient education is important. "Most refractive surgery patients haven't thought about phakic IOLs," he says. "Most of their friends have had LASIK or PRK, so we need to have a plan for how to talk to patients when they have never heard of phakic IOLs. Otherwise, they'll seek out other docs to try to find someone who will do LASIK or PRK for them, despite the fact that you feel like a phakic IOL is definitely their best option. I try to give patients a definitive answer rather than a choice. In this situation, if I feel that a phakic IOL is best, I don't really give them the option of PRK or LASIK."

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To help patients understand the procedure, Dr. Hardten tells patients that the implant is like getting a contact lens implanted in their eye. "I let them know that, because of their age, their natural lens still has range of focus, so the implant goes over their natural lens," Dr. Hardten says. "This provides a better outcome than we would be able to achieve with LASIK or PRK. Most patients understand, but it's not uncommon for them to return for a second discussion."

Preop and Intraop Tips

Dr. Holz says that sizing is everything with phakic IOLs. "I always tell patients there's a small chance of having the lens removed and replaced with a lens that's going to be more appropriate for the size of their eye," he says. "You must be fastidious about your white-to-white measurements. It's a great idea to check sulcus diameter with ultrasound biomicroscopy as a corroborative measurement.

"The company has developed nomograms to help surgeons determine which lens is the appropriate size for a particular eye," he continues. "The ICL must be well away from the crystalline lens, but it has to not be so vaulted that your lens creates a posterior pushing glaucoma mechanism because you're closing the angle. In the rare situations where the lens is vaulted so much that it's pushing posteriorly against the iris and closing the angle it should be replaced if you have elevated intraocular pressures that persist."

Lance Ferguson, MD, in practice in Lexington, Kentucky, strongly recommends general anesthesia. "Even minor movement from the patient can lead to disaster," he says.

Dr. Hardten does most of his phakic IOL cases under topical anesthesia, but does them in the ambulatory surgery center, where he can use IV sedation as needed. "Small amounts of IV sedation like we use for cataract surgery keep patients much more comfortable," he says. "Then, I rinse the viscoelastic out with bi-manual irrigation/aspiration, which I think reduces the tendency to have issues like postoperative IOP rise, and is easy to do in the ambulatory surgery center by removing all of the viscoelastic at the end of the case. Having the pupil reasonably well-dilated, but not extremely dilated, is very helpful in being able to tuck the haptics of the Visian underneath the iris without necessarily having it come back up out of the sulcus into the anterior chamber. We use just one drop of tropicamide preoperatively. Intraoperatively, I have a little bit of epinephrine in my lidocaine solution, and that typically provides reasonable dilation in most of these patients."

Dr. Ferguson recommends that either the surgeon or a trusted tech load the IOL. "It's kind of tricky to load," he says. "You must align two tiny apertures in the ICL to ensure you've achieved the proper orientation. If aligned properly, you prevent the ICL from flipping over during injection, and it's imperative to avoid any unnecessary manipulation of the ICL in the anterior chamber. You can confirm proper alignment by looking for symmetrical delivery of the wingtips as they pop out of the injector. Stay anterior to the iris and back the injector out a little bit as you deliver the tips of the back haptic. Once the lens is in the eye and properly oriented, you can add more OcuCoat (Bausch + Lomb) to give yourself additional working room. Then, use a paddle to position the tips of those haptics posterior to the iris. The paddle is the perfect instrument for this maneuver, as its curvature allows contact solely with the tips of the plate haptics and avoids any touch of the central optic, as posterior displacement could press against the crystalline lens and possibly lead to cataract formation."

According to Dr. Holz, phakic IOL implantation is quick and easy. "One pearl is to make a peripheral iridotomy either in the clinic or intraoperatively," he says. "My preference is to do this with a vitrector at the time of surgery because it's so quick, easy, and reliable. However, this will soon no longer be necessary. The EVO ICL *[see sidebar, left]* with a small port in the center will soon be available in the U.S., which we're all looking forward to. It will have a very small drain for aqueous in the center of the lens, so peripheral iridotomies will no longer be needed."

Dr. Holz recommends dilating eyes with tropicamide. "Only use tropicamide, so the pupil comes down a little faster with Miochol (Bausch + Lomb) instillation during surgery," he says. "Other pearls would be loading the lens yourself under the microscope. It's not the easiest or most intuitive loading system, so most technicians aren't able to do it." Dr. Hardten also prefers to load the IOL himself, especially because he doesn't

FIRST LOOK: VISIAN ICL V4C WITH CENTRAFLOW

Although this lens, brand name EVO, is still in trials, it's been found to provide results similar to its predecessors for correcting moderate to high myopia and maintaining safe IOP levels without the need for an iridotomy.[1]

This lens has a central artificial hole called the KS-AquaPort that was added to the center of the ICL optic to improve aqueous humor circulation in the eye. This eliminates the need for a preoperative peripheral laser iridotomy or intraoperative peripheral iridectomy, which the company says simplifies the surgical procedure and significantly reduces the complications associated with iridotomy.

A retrospective cohort study included 17 eyes implanted with the ICL V4b model and 18 eyes implanted with the ICL V4c model. The mean preoperative spherical equivalent refractions were -7.48 ±5 D for the V4b design and -8.66 ±4.2 D for the V4c design.

Three months postoperatively, the mean uncorrected distance visual acuities were -0.09 ±0.12 logMAR with the V4b and -0.07 ±0.11 logMAR with the V4c. Mean distances between the ICL and the anterior crystalline lens surface were 557 ±224 µm for the V4b and 528 ±268 µm for the V4c. The mean IOPs were 13.7 (V4b) and 13.3 mmHg (V4c) after one week and 14.7 (V4b) and 15.1 mmHg (V4c) after a month. No significant differences in IOP were observed within or between groups during the follow-up period.

1. Higueras-Esteban A, Ortiz-Gomariz A, Gutierrez-Ortega R, et al. Intraocular pressure after implantation of the Visian Implantable Collamer Lens with CentraFLOW without iridotomy. Am J Ophthalmol 2013;156:4:800-805.

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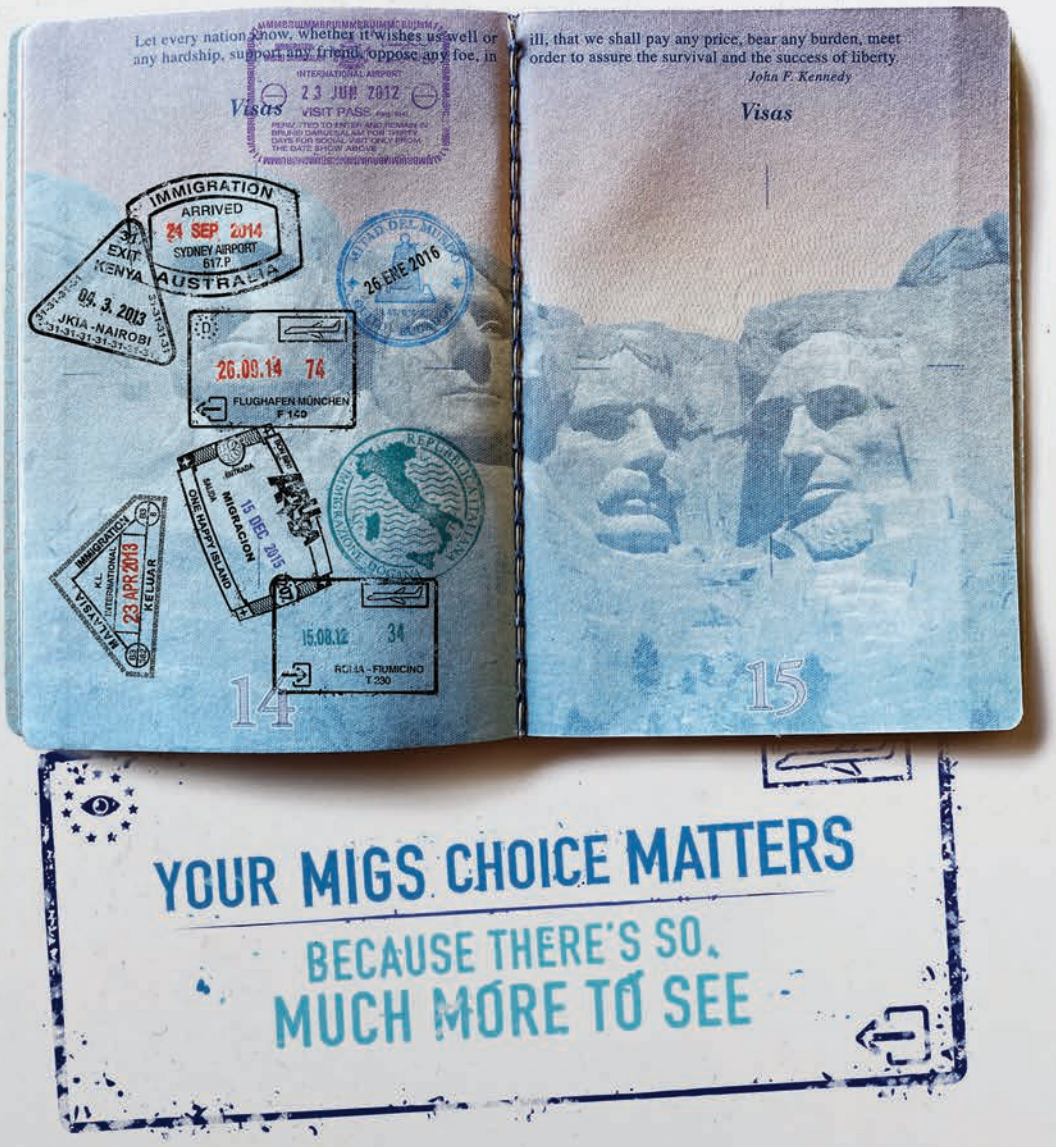

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Dr. Hovanesian adds that one of the most challenging parts of the procedure is avoiding touching the crystalline lens with anything but viscoelastic. "If you're going to touch it, do so only very peripherally and not in the optical center of the crystalline lens," he advises. "There are plenty of videos online showing implantation. Following the recommendations of the manufacturer and the videos that you see is really the best advice."

Dr. Hardten prefers to do each eye separately. "Usually, we separate them by a few days or a week, depending on patient preference," he explains. "I operate out of two different locations. I'm in each of my locations once a week, so some of the patients are willing to travel between locations [to have the surgery] a couple of days later, but I typically do them about a week apart. Because I got all of my measurements the first time around when they'd been out of their contact lenses, I let them wear their contacts in between the two eyes, which solves most of the issues with the anisometropia."

Postop Pearls

According to Dr. Holz, the toric version of the phakic IOL is different from typical toric IOLs implanted for cataract surgery. "The lens toricity is built into the [phakic] lens to match the patient's astigmatism," he says. "The lens is implanted in the horizontal meridian and rotated only up to 22 degrees off the 180-degree axis to ensure proper sizing for the sulcus and that the peripheral iridotomy isn't blocked. The toricity is imprinted in the lens at the desired axis of the patient's astigmatism so the lens only has to be rotated minimally from the horizontal meridian. This is quite different from the current version of toric intraocular lenses that we implant for cataract surgery [which need to be rotated in order to line up the toric-correction axis of the lens with the patient's steep axis.]"

Outcomes

According to Dr. Hardten, the recovery process is quick, especially with the Visian implant. "These patients with extreme myopia are 20/20 or 20/25 on day one, and they tend to be very stable over time," he avers. "It's just impressive how happy patients are. It's sort of like they forgot to take their contacts out."

He recommends that patients be seen annually after implantation of a phakic IOL. "Their natural lens will grow over time, and that growth can then change the anatomical relationships inside the eye," he warns. "The natural lens can push forward on the implant, so it can shallow the anterior chamber. These patients need to be observed for glaucoma, cataract formation and endothelial cell issues.

"I've been doing phakic IOLs now since 2000," he adds, "and it's kind of fun to see some of the patients coming in 20 years later who still have the 20/20 vision they've had from day one. These patients will eventually develop cataracts around age 60 to 65, like everyone else. At that point, we remove the phakic IOL and the crystalline lens, and implant an IOL."

The Future of Phakic IOLs

According to Dr. Holz, there's a growing subset of patients with extreme myopia. "These are high myopes who absolutely hate their glasses," he says. "They often run into problems with contact lenses because they overwear them, because they can't deal with wearing glasses, even at home. They're sort of in a pickle refractively, and so we need to have a refractive solution for them.

"For patients in their early 40s and younger, the retinal detachment risks associated with clear lens exchanges are too high, and they also stand to lose their accommodation with these refractive lens exchanges," Dr. Holz continues. "So, for those patients who are younger than 50, we think about doing phakic IOLs because they get to preserve their accommodation, and there's a lower chance of retinal detachment. Satisfaction rates are quite high with this modality. And we can look forward to further advancements in this technology, since the need for these lenses certainly isn't going away." ◀


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ARTIFICIAL INTELLIGENCE: THE BIG QUESTIONS

Experts discuss the latest innovations and weigh in on the challenges of AI.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

Artificial intelligence is gaining traction in nearly every field and industry by helping people process data and make decisions. In ophthalmology, experts say it has a bright future and the potential be a valuable physician-assistance tool. "We're inundated with data and imaging and other diagnostic criteria for our patients, and we need to be able to process all of that information very quickly," says Rishi P. Singh, MD, of the Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, and a professor of ophthalmology at the Lerner College of Medicine in Ohio. "AI can help us make good clinical decisions, increase reliability and improve the quality and safety of our patients' outcomes and ensure we don't miss something inadvertently. We aren't immune from transposition, data or interpretation issues. Anyone can make a mistake, especially in a high-volume practice."

However, the technology isn't immune from certain challenges. "For the AI systems to become part of our treatment algorithm, we need to have a sophisticated infrastructure that can accumulate all the information mounted to the cloud and then communicate to the physician and the patient if there's an alert and the patient needs to see a retina specialist," explains Anat Loewenstein, MD, director of the ophthalmology division at Tel Aviv Medical Center and associate dean of the Sackler Faculty of Medicine at Tel Aviv University. "Adoption by patients, especially elderly people, is another important potential hurdle. There's also a lack of reimbursement patterns and regulatory pathways for AI-assisted managed care, and the physician will need to oversee a huge amount of data. This may interrupt patient flow and become problematic."

Here, experts review the two FDA-approved AIs, and algorithms in development, and discuss the unique challenges AI technology will face before widespread implementation.

FDA-approved Devices

There are currently two FDA-approved devices for diabetic eye-disease screening. SriniVas R. Sadda, MD, FARVO, a professor of ophthalmology at the David Geffen School of Medicine at UCLA and the director of Artificial Intelligence & Imaging Research at Doheny Eye Institute, says remote disease screening was a natural entry point for AI technology, since screening systems have many time delays. "Data must be transmitted somewhere, experts must evaluate it and then get information back to the patient, and that patient needs to be scheduled to see a specialist if they have significant disease," he says. "Every time there's a delay in the system, the chance the patient doesn't show up for the next appointment increases

This article has no commercial sponsorship.

Dr. Sadda has NEI/NIH grants with Eyenuk. He is a consultant for Optos, Heidelberg Engineering and Centervue and receives research imaging instruments from Optos, Heidelberg Engineering, Centervue, Nidek, Topcon and Carl Zeiss Meditec. **Prof. Loewenstein** receives grants from Roche and Novartis and is a consultant for Allergan, Bayer, WebMD, NotalVision and Beyeonics. **Dr. Singh** is a consultant for Novartis, Genentech, Regeneron, Bausch + Lomb, Gyroscope and Asclepix. He also receives research support from NGM Biopharmaceuticals. **Dr. Wang** has no relevant commercial financial disclosures.

because they didn't get the information. Theoretically, AI can give a patient an answer instantly, to determine whether or not they need to be referred right away or whether they can wait a year. That's why AI is such a game-changer."

IDx-DR (Digital Diagnostics) was the first FDA-approved autonomous AI device in any field of medicine. It's designed to detect diabetic retinopathy and diabetic macular edema. Since its approval in 2018, IDx-DR has been used at Stanford, Johns Hopkins, the Mayo Clinic and in Delaware supermarkets to screen patients for disease. The device is indicated for adults over 22 who haven't been previously diagnosed with DR. Currently, IDx-DR is available on the Topcon TRC-NW400 digital fundus camera. IDx-DR was validated against clinical outcomes in a 2018 study where it demonstrated 87-percent sensitivity and 90-percent specificity for detecting more-than-mild DR.[1] Additionally, the algorithm, which was trained to detect biomarkers, performed well on a diverse population.

The IDx-DR from Digital Diagnostics autonomously detects diabetic retinopathy in adults.

EyeArt (Eyenuk) is another autonomous AI that's FDA-approved for detecting more-than-mild and vision-threatening DR in adults. Like the IDx-DR, EyeArt is approved for patients who are diabetic without any known retinopathy. The cloud-based AI system is compatible with two nonmydriatic fundus cameras, the Canon CR-2 AF and the Canon CR-2 Plus AF. In the clinical trial, EyeArt results were compared to human graders at the Wisconsin Fundus Photograph Reading Center. The pivotal trial achieved 96-percent sensitivity and 88-percent specificity for detecting referral-standard or more-than-mild DR. For vision-threatening DR, EyeArt demonstrated 92-percent sensitivity and 94-percent specificity.[2]

"Importantly, eyes that had significant or worrisome retinopathy—ETDRS level 43 or higher, for example—were all correctly identified as more than mild," says Dr. Sadda, one of the trial investigators. His team at UCLA conducted the initial training of the EyeArt algorithm through NEI/NIH grants with Eyenuk.

These autonomous AI-based screening devices do a good job of detecting referable DR, but single-disease expertise is also a limitation. "Diabetic retinopathy is a very complicated disease," says Dr. Singh. "It has implications with regard to cataract, glaucoma and refractive error, among others. None of these other conditions is addressed by these AI platforms."

He doesn't foresee AI completely replacing DR screening in the near future, unless someone develops a device that can assess all of these conditions. "Nevertheless, AI screening will greatly benefit underserved populations," he says.

Sophia Ying Wang, MD, an assistant professor of ophthalmology and primary investigator with the Ophthalmic Informatics and Artificial Intelligence Group at Stanford University, agrees that remote screening, while imperfect, will be able to identify many more cases of early retinal disease in populations where it might otherwise go undetected. "We may be able to improve ophthalmic outcomes in this way," she says.

Natural Language Processing

There are other ways to predict patient outcomes besides analyzing images. Natural language processing

ARTIFICIAL INTELLIGENCE KEYWORDS

Artificial intelligence is a broad field. Here are a few key definitions:

• ***Artificial intelligence.*** Definitions vary, but in general AI consists of systems that seem to mimic some human capabilities such as problem-solving, learning and planning through data analysis and pattern identification.

• ***Machine learning.*** A subfield of AI that uses computer algorithms to parse, learn from and apply data in order to improve itself and make informed decisions. Machine learning makes your Netflix recommendations possible. It still requires occasional guidance if it turns up an inaccurate prediction.

• ***Deep learning.*** A subfield of machine learning that uses a layered structure of algorithms to create a neural network. This allows a machine to make decisions independently from humans. The algorithm can detect an inaccurate prediction on its own using its neural network.

• ***Neural networks.*** Sometimes called artificial neural networks (ANNs), neural networks are computing systems modeled after the human brain and are central to deep learning. They're made up of node layers, each containing an input layer, a hidden layer(s) and an output layer. Neural networks rely on training data to learn and improve their accuracy. Google's search algorithm is a type of neural network.

—CL

is a subfield of artificial intelligence that's focused on understanding human language as it's written and spoken, explains Dr. Wang. "My research is particularly focused on using techniques in natural language processing to understand free-text clinical notes in electronic medical records," she says. "Physicians spend so much time documenting important clinical details in these notes. There's a wealth of information about patients in clinical notes that isn't captured elsewhere (such as in billing codes or demographics), and it's difficult to extract and compute without the aid of natural language processing techniques.

"I believe that with more detailed clinical information about patients, we can build algorithms that have better performance when predicting ophthalmic outcomes, such as glaucoma progression or visual prognosis," she says. "If we could build better predictive algorithms, effectively a 'crystal ball' for the future of the patient, that could be enormously helpful for doctors personalizing their therapies according to the likely prognosis of the patient."

In a recent paper, Dr. Wang explored different methods of representing clinical free-text ophthalmology notes in electronic health records to build an algorithm that predicts patients' visual prognosis.[3] "Some patients with low vision don't regain significant vision quickly despite initiation of therapy—like a wet AMD patient receiving anti-VEGF injections who still sees poorly after several months," she explains. "These patients may benefit from early referral to low-vision rehabilitation services, rather than waiting for their therapy course to be complete.

"If an algorithm could predict that a year later they'd still have poor vision, then perhaps a clinical-decision support system could automatically prompt a referral to low-vision services, rather than having to delay for months waiting to see the results of the therapy before getting a referral," she continues. "There are many clinical details in the notes that can provide clues to a patient's prognosis, such as specific exam findings (geographic atrophy, cataract, other comorbidities) and other details. In our work, we're exploring ways to take that human-readable text and turn it into computer-readable numbers [a method known as word embedding] that could then contribute to algorithms predicting a patient's prognosis, taking into account all of the special language that ophthalmologists frequently use."

EyeArt (Eyenuk) is a cloud-based autonomous AI system that can detect clinically significant macular edema in addition to diabetic retinopathy.

The deep-learning model trained on domain-specific word embeddings performed better using ophthalmology word embeddings than general word embeddings. These ophthalmology word embeddings are now publicly available for research.

Image Processing

Dr. Wang's group is also involved in a project for cataract surgical videos, involving "computer vision" or image processing techniques. "The idea is to train an AI algorithm to be able to automatically detect what steps are being performed in a surgical video at any given moment (e.g., use of trypan blue, capsulorhexis, phacoemulsification or anterior vitrectomy). We also want to be able to detect key landmarks of the eye (such as where the limbus or the pupil margin are) and where important instruments are inside the eye (such as where the second instruments or the phacoemulsification tip are)."

She says that recognizing what's happening in a cataract surgery could be very helpful for many different tasks. "For trainee surgeons, recognizing how long each step is taking or what path the instruments are taking in the eye could prompt automated feedback metrics to help them grow into better surgeons. Or, perhaps one day a computer vision system like this could form the basis of robotic-assisted cataract surgery that could warn surgeons just before they're about to break the capsule and thus avert complications. There are many potential-use cases."

Other AI in Development

Using AI to obtain better images, helping ophthalmologists process large amounts of data or giving patients the ability to image themselves at home are all on the horizon. Many companies are working on AI technologies in the United States. Here are just a few:

• ***Self-imaging.*** Several self-operated OCT systems have shown promising results, says Prof. Loewenstein. She says that home OCT monitoring will contribute to increased accuracy and individualized treatment, as well as reducing

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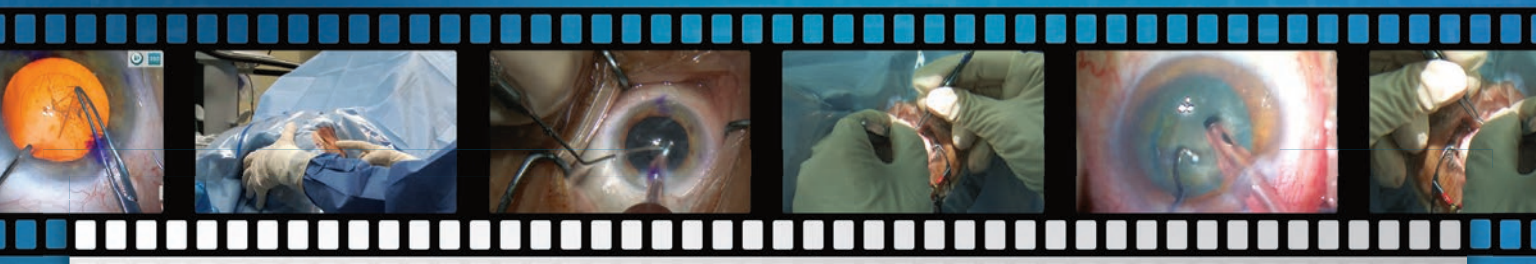

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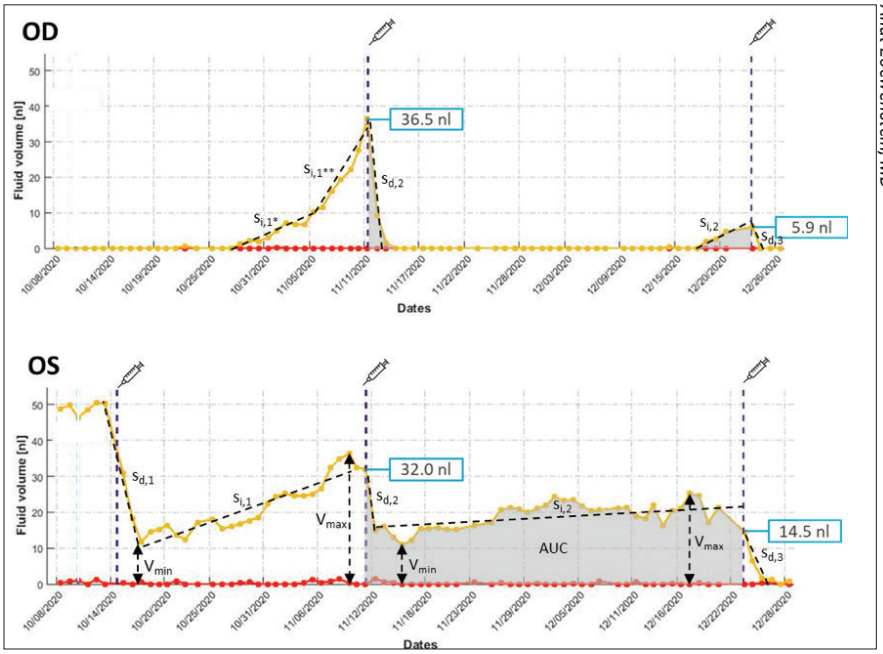

Anat Loewenstein, MD

Figure 1. Intraretinal fluid (red curve) and subretinal fluid (yellow curve) volume trajectories from Notal OCT Analyzer (NOA) segmentation of daily home OCT self-images of a patient's right and left eye. Vertical dashed lines indicate the dates of intravitreal injections. Retinal fluid exposure described by the area under the curve (AUC) between treatments differs significantly between eyes, despite similar fluid volumes measured on the day of office treatment visits, illustrating the medical insights gained from daily OCT imaging at home. Minimum (Vmin) and maximum (Vmax) fluid volume, as well as inclining (si) and declining (sd) slope of fluid volume trajectories, describe disease activity and treatment response, in some cases broken up in distinct phases of fluid volume increase (si,1*, si,1) during a treatment cycle.**

time intervals between fluid recurrence and the next treatment.

—Using the time-domain full-field OCT prototype device SELFF-OCT, at least 76 percent of the study population could obtain at least one gradable image.[4]

—A sparse-sampling OCT prototype device, the MIMO_02, has successfully identified ocular comorbidities of AMD patients.[5]

—NotalVision's OCT Analyzer (NOA) is a spectral-domain-based OCT that enabled 90 percent of patients with wet AMD (mean age: 74) to perform successful self-imaging in a study.[6,7] "When the interpretation of retinal fluid by human graders was compared to the interpretation of the NOA, the agreement on retinal fluid recurrence was 97 percent and the agreement on absence of retinal fluid was 95 percent," says Prof. Loewenstein, who is also a consultant to NotalVision. "These studies are exciting because they contribute to the treatment of chronic ocular conditions, which aren't easily managed and require constant monitoring, placing a burden on patients, their caregivers and clinicians as well."

The NOA is an AI software application trained to automatically detect retinal fluid. It quantifies intraretinal and subretinal fluids using cube scans generated from B-scans on OCT (*Figure 1*). With the cube scans, B-scans are ranked by size of fluid area and *en face* fluid thickness maps produced by the system. Prof. Loewenstein says the system uses the following steps: (a) An accurate localization of the ILM and RPE areas, (b) fluid identification using standard imaging, (c) machine-learning-based classification of fluid-filled areas and (d) quantification of the retinal fluids (fluid volume).

A 2021 study of the NOA evaluating its performance included eight eyes of four patients (BCVA 20/50).[8] Patients performed daily self-imaging for one month and managed to obtain self-imaging 94 percent of the time. Prof. Loewenstein says retinal fluid was found in 93 of the 211 scans: intraretinal and subretinal fluid in 49 and 44 scans, respectively. Mean volume of fluid recurrence detection was 1.6 nL. There was also a 94.7-percent level of agreement between human graders and NOA on fluid status.

Prof. Loewenstein says the at-home device provided insights regarding the diagnosis of macular neovascularization, its classification, localization of retinal fluid in wet AMD, conversion from dry to wet AMD, visual acuity prognosis and retreatment decisions. She says additional steps such as grouping by uniform patient characteristics (same AMD stage and treatment regimen) and robust validation of the algorithm on larger populations and over longer periods of time are needed to improve the AI system.

• ***Predicting macular thickness from fundus photos.*** A proof-of-concept study published in 2019 assessed Genentech/Roche's deep learning model, which could predict key quantitative time-domain OCT measurements related to macular thickness from color fundus photographs.[9] The best deep learning model was able to predict central subfield thickness ≥250 µm and central foveal thickness ≥ 250 µm with an AUC of 0.97 and 0.91 (95% CI), respectively. To predict CST and CFT ≥400 µm, the best deep learning model had an AUC of 0.94 and 0.96, respectively. The researchers say this model could enhance DME diagnosis efficiency in teleophthalmology programs.

• ***Automated B-scan reading.*** A preliminary study presented by Zeiss in an ARVO 2021 poster session evaluated an AI-based tool

for reading B-scans.[10] The researchers trained a deep learning algorithm on 76,544 B-scans of 598 glaucoma patients and 25,600 B-scans of 200 healthy subjects to predict if a given B-scan might be "of interest" based on ground-truth labels from retinal specialists in healthy eyes and eyes with retinal pathologies. The algorithm generated 100-percent and 79-percent agreement in healthy and glaucomatous eyes, respectively. Four cases of disagreement resulted from unusual retinal curvature, unusual contrast in the vitreous and other false positives with inference scores near the algorithm cut-off.

• ***Expert-level 3D diagnostic scan reading.*** In 2014 Google acquired DeepMind, one of the world's leading AI companies. Varun Gulshan, PhD, and his colleagues at Google put the Inception-v3 convolutional neural network proposed by AI researcher Christian Szegedy, PhD, and colleagues to work on the EyePACS-1 dataset (n=9,963 images) of routine DR screening images in the United States and India, and the Messidor-2 dataset (n=1,748 images). In the paper, published in JAMA in 2016, the referable DR algorithm had an AUC of 0.991 for EyePACS-1 and 0.99 for Messidor-2. In 2019 they announced real-world clinical use of the CE-marked algorithm at Aravind Eye Hospital in Madurai, India.

Google DeepMind is working with Moorfields Eye Hospital to develop algorithms for early DR and AMD detection. In 2016, the group signed a formal research collaboration agreement to share anonymized historical OCT scans. Their proof-of-concept study was published in *Nature Medicine* in 2018, which demonstrated expert-level performance with 3D diagnostic scans for the first time.[11]

Google DeepMind also improved AI interpretability, part of a problem known as the "black box." This is often encountered in "unsupervised" approaches. "The AI makes a prediction, but we don't always know why," says Dr. Sadda. "A classic example of this in AI is an algorithm that predicted dog breeds. It identified certain dogs as being Alaskan huskies, but it was making the prediction not because of specific dog features but because of the background—it always saw huskies in the snow. It got the right answer for the wrong reasons."

Susan Ruyu Qi, MD, an ophthalmology resident and Masters student in clinical informatics management at Stanford, explains that Google approached the black box problem using a two-step process of segmentation and classification instead of training a single neural network to identify pathologies from images.[12] It has since undergone adjudication improvements with regard to grading.[13] Google also collaborated with Optos in 2017 to develop early-detection algorithms for diabetic eye disease, likely making use of Optos' ultrawide-field

fundus imaging.

• ***Predicting disease progression.*** AI is predicted to play a major role in the fast-approaching era of personalized medicine and individualized patient care. At UCLA, Dr. Sadda and his colleagues are working on ways to predict patient outcomes using AI. "We've developed algorithms that can predict development and progression of atrophy in AMD," he says. "We've also developed a similar algorithm for predicting progression in Stargardt's disease, which is the biggest cause of juvenile macular degeneration."

• ***Uncovering new biomarkers.*** "In our group, we're particularly interested in how we can automatically detect features we believe are associated with higher risk for disease progression," Dr. Sadda continues. "We even take it a step further and let the technology make a prediction based on its own assessment so we can reverse engineer its decision and learn about predictive features we haven't previously understood. Some call this 'unsupervised classification,' and it may open up a space where AI can help us gain new insight into disease mechanisms and pathology."

Algorithm Imperfection

Even though these algorithms will be rigorously tested against a large dataset that's hopefully representative, the question always remains: will it work for the specific patient in front of you? "It might not," says Dr. Sadda. "All algorithms will have a particular sensitivity and specificity, and we'll still have to use our own clinical judgment. These devices will likely be employed as physician assistance devices initially. They're not perfect."

"With any disease detection system, we have to think carefully about the population on which the systems were developed and validated, and then in what population the system is going to be deployed,"

A patient undergoes screening for diabetic retinopathy with the IDx-DR, which is intended for use mainly in primary care settings.

says Dr. Wang. "It may not be reasonable to expect that a system developed in the United States should work just as well in Mumbai or Johannesburg, and vice versa, as the underlying patient population and disease characteristics could be quite different. If one purported goal of AI is to bring 'personalized medicine' to patients, it may be entirely appropriate, and indeed desirable, to have AI algorithms that work well for the specific population that they are going to be deployed in, rather than trying to aim for an elusive goal of 'one system that works for the whole world.' "

Practical Use Questions

It's important to remember that disease detection and screening isn't an end in itself. "We'll have to think carefully about what we're planning to do to help patients who screen positive," says Dr. Wang. "Is there an intervention that could help improve their outcomes? Are they able to access this intervention? Is the infrastructure set up to facilitate follow-up?" Here are some other questions to consider:

• ***Can you use it?*** Dr. Singh says that providers will need to understand how the algorithms work. "We have to be able to explain and understand the algorithms, comprehend outcomes and potentially troubleshoot if there's a problem," he says. "They can't be 'black box' algorithms. What will you do if the data isn't showing up? Are you able to support the software? Do you understand the AI might require significant server space or integration with a camera? For health-care organizations, they'll also need to understand the financial costs and potential benefits associated with AI and then decide whether they want to be involved with such a device."

• ***How will you choose among the AI technologies?*** With so many options in development by different companies, how will physicians and health-care organizations be able to make the most educated choices? Companies will present their clinical trial data, but how can you compare the numbers from one study to the next? The first set of international standards for reporting of clinical trials for AI was released in September 2020.[14] The reporting guidelines expand upon the SPIRIT 2013 and CONSORT 2010 frameworks to boost robustness and transparency.[15,16] "We hope that eventually there will be universal standard test decks from the FDA or other regulatory bodies that new algorithms can be tested against," says Dr. Sadda.

• ***How will software updates be regulated to protect patients?*** "Another important thing to consider is that these algorithms continue to improve as they learn, so the version of the algorithm you're using may be very important," he continues. "This will also be a challenge for the FDA and regulatory bodies. Will they need to pre-approve every little change in the software? We're used to a new device that gets approved and doesn't change for some time until the next generation. But AI is very incremental and undergoes continuous improvement. How do you regulate this so

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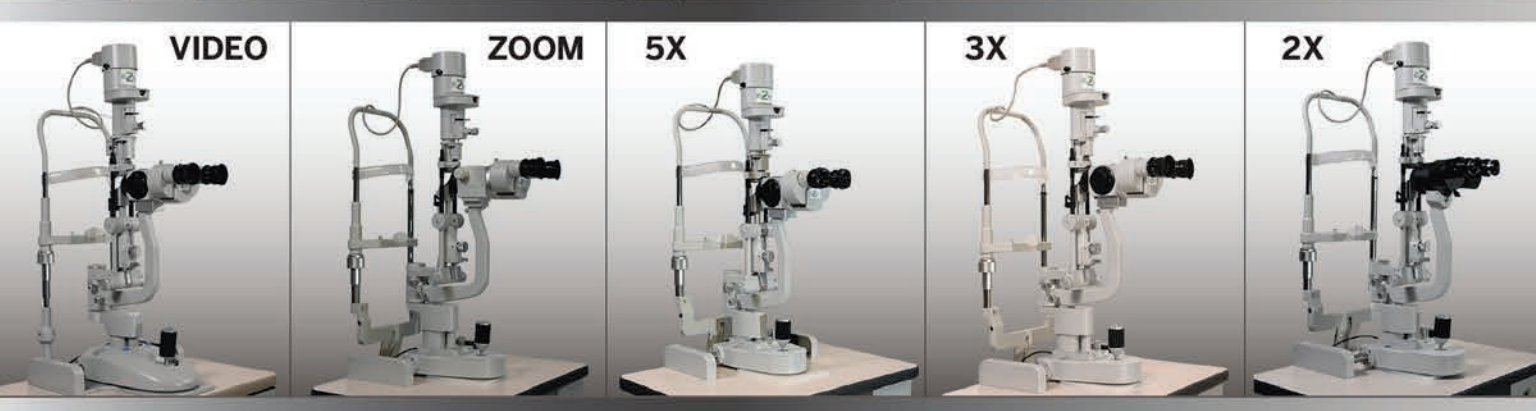

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HIGHLIGHTS FROM THE 2021 OPHTHALMIC AI SUMMIT

The Ophthalmic AI Summit took place virtually this year in June. Rishi P. Singh, MD, of the Cole Eye Institute, Cleveland Clinic, Ohio, and one of the Summit's panel discussion moderators, shares the following highlights:

• ***AI/Reader Alignment.*** "Ursula Schmidt-Erfurth, MD, demonstrated in her talk on geographic atrophy and AI that there's a disconnect between the way we interpret images and the way an AI platform interprets images. There's a higher degree of alignment between the AI and true outcomes versus grader reading, which is important to keep in mind."[1] She noted that deep learning can empower experts to understand images better. She uses the Vienna Fluid monitor algorithm in her macular clinic to manage nAMD patients.

• ***EHR Data and Glaucoma.*** "Sally L. Baxter, MD, MSc, pointed out in her talk on predictive modeling of glaucoma progression using EHR data that AI has huge potential in glaucoma too. We're heavily focused on retina right now, but data interpretation and analysis will also be incredibly important to show disease progression and changes over time in glaucoma.[2]

• ***Telemedicine.*** "David Myung, MD, discussed the impact of teleophthalmology and AI on diabetic eye exam adherence—particularly low-cost reading methods in public health forums and how that will benefit patients."[3]

In January 2021, the 92229 CPT code for AI exams went into effect.

—CL

1. Schmidt-Erfurth U. GA diagnosis and therapy by AI. Presented at the Ophthalmic AI Summit, June 2021.
2. Baxter SL. AI and predictive modeling of glaucoma progression using EHR data from the NIH All of Us Research Program. Presented at the Ophthalmic AI Summit, June 2021.
3. Myung D. Impact of teleophthalmology and AI on diabetic eye exam adherence in Bay Area primary care clinics during COVID-19. Presented at the Ophthalmic AI Summit, June 2021.

that it protects patients? This will be a major challenge in the future."

On the Same Page?

AI referral patterns are fairly straightforward—if a patient has any amount of potential DR, they're usually referred to an ophthalmologist or retinal specialist. However, this may result in too many referrals of patients who could otherwise be managed by optometrists or wait a year for another retinal exam. "The issue with these platforms is that it's not as simple as saying 'always refer the patient,' " says Dr. Singh, who is a member of the ASRS Artificial Intelligence Task Force. "Many times the AAO and AMA recommend annual referral. If the patient has only a small amount of retinopathy they may not necessarily need to do anything at that time."

That's where the disconnect is, he says. "I've talked to the AAO and ASRS about setting up more standards for working with AI platforms, to ensure these platforms understand the referral patterns the organizations follow. A lot of these platforms don't necessarily involve the Academy or ASRS in their development or strategic planning, so as a result, recommendations come out of the machine that aren't aligned with what we're doing. We have the opportunity in AAO and ASRS to work with AI platforms and develop better focus on referral patterns and interpretation. We want to ensure the AI reflects what we say in clinical practice too. They need clinical validation or alignment with what we do in practice."

Dr. Sadda says it's important that ophthalmologists take an active role in shaping how AI technology becomes part of the field. "We need to have some control over how these technologies are deployed," he says. "We need to make sure they're safe and provide the best care for our patients, whatever the proposed application is. Ophthalmologists must be proactive." ◀

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Cataract Surgery in the Presence of Hypotony

A very low intraocular pressure can have negative consequences when performing cataract surgery. Here's help.

ERIN A. BOESE, MD
IOWA CITY, IOWA

Performing cataract surgery in a patient who has an overfiltering trabeculectomy is a scenario we all hope to avoid. Nevertheless, it's good to be prepared, because sooner or later every glaucoma or cataract surgeon will be faced with such a patient.

A trabeculectomy can be very effective for lowering the intraocular pressure when the normal outflow channels aren't functioning well. If a trabeculectomy works too well, however, the result can be hypotony and its attendant sequelae. The visual consequences of hypotony are problematic, and measures must be taken to increase the IOP. Unfortunately, fixing hypotony is challenging; it's much easier to lower IOP in a glaucoma patient than it is to raise it. Furthermore, care must be taken to not elevate the IOP too much in patients with known glaucomatous damage.

Facing hypotony in a patient with a visually significant cataract introduces even more variables and challenges. Here, I'll offer some suggestions for managing a patient in this situation, to increase the likelihood of achieving the best possible outcome when performing cataract surgery.

Asking Key Questions

When you're planning to do cataract surgery on a patient with an overfiltering, hypotonous trabeculectomy, preoperative considerations are arguably the most important step. It's important to ask four main questions before you operate on these patients:

• ***Is this really hypotony?*** First of all, you need to decide whether your patient is hypotonous—meaning that the patient is symptomatic from the low IOP. Symptomatic hypotony isn't associated with a specific IOP; some people may be hypotonous at a pressure of 7 mmHg, while others may not have signs of hypotony despite an IOP of 2 mmHg.

Population-based normative values indicate that an IOP of 10 mmHg or less is below "normal."

More patients may develop complications of low IOP at 5 mmHg or less, which is a threshold for hypotony often used in clinical trials. However, these numerical thresholds don't reflect the reality that some patients may have lower measurements of IOP but not have any ocular complications due to the low IOP.

The presence of symptomatic hypotony is indicated by clinical signs such as decreased vision, hypotony maculopathy (which you can see on exam or OCT), and sometimes choroidal effusions or corneal folds. If your patient has an IOP of 2 or 3 mmHg, but their visual acuity is 20/20, they have no visual distortions and they're happy as a clam, that's not hypotony.

Whether or not the signs of hypotony appear seems to depend on how much a given eye can tolerate at a given pressure. That means that hypotony is very patient-dependent. That's why your first step is deciding whether the low IOP you're finding is associated with hypotony.

Once you've decided that the patient's IOP really is lower than it should be, the next three questions become crucial:

• ***How long has the patient been hypotonous?*** If it's been more than six months or a year, there may be some irreversible components to the hypotony—especially hypotony maculopathy, which can lead to blurred, distorted and decreased vision. If the hypotony maculopathy has been present for a long time, the odds of a perfect outcome are diminished, so you need to make sure you set the patient's expectations appropriately.

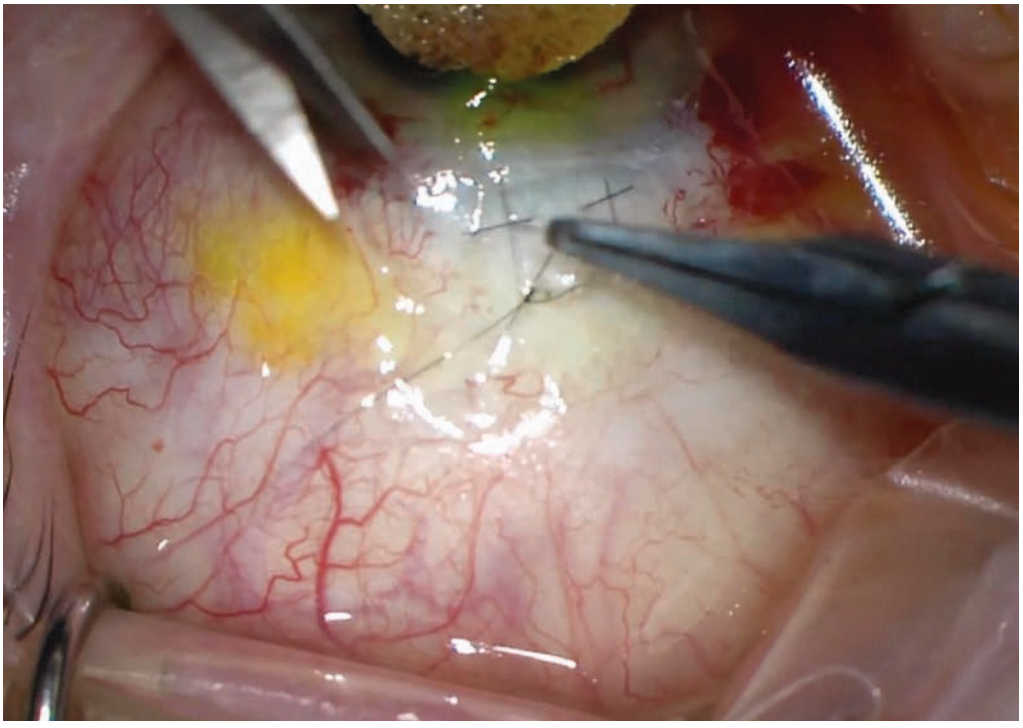
• ***How much of an IOP increase are you looking for?*** If you're starting from 6 mmHg and looking to nudge the IOP up a little bit, you're going to use different techniques than if you're starting at a pressure of 0 or 1 mmHg and trying to increase that pressure to 10 mmHg. (More about those techniques in a minute.)

How much you need to raise the pressure will help you answer the next question:

• ***Should I address the hypotony before, during or after the cataract surgery?*** If you're trying to increase the IOP a lot, I'd argue you'll be better off trying to accomplish that

This article has no commercial sponsorship.

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



Performing a surgical revision of the bleb is a good way to proceed if you need a significant increase in IOP to avoid the consequences of doing cataract surgery on a hypotonous eye. This should be done prior to the cataract surgery to ensure that optical measurements are made with the eye at a normal pressure.

beforehand, to ensure the accuracy of your IOL calculations. We know that the axial length of the eye can increase when IOP increases. That means that if you measure the axial length before addressing the hypotony and the pressure is normalized later, your cataract surgery will lead to a myopic surprise.

Studies have shown that in the presence of a normally functioning trabeculectomy bleb the axial length can increase by 0.1 to 0.2 mm when the eye pressure increases. That effect is magnified in the presence of hypotony and its resolution. For example, I had a patient who had refractively very similar eyes prior to a blunt injury to her left eye that resulted in a cyclodialysis cleft and an IOP of 2 mmHg. When I did her IOL calculations, the axial length in that eye was nearly 3 mm shorter than in the right eye. *(See figure, p. 78.)* If I had just used those measurements to determine what IOL power to implant, without taking the hypotony into consideration, the numbers would have called for an 8-D stronger IOL than she actually needed after the hypotony resolved. She would have been pretty unhappy with me!

The other thing that can be altered by hypotony is the corneal shape; keratometry readings can shift significantly. As a result, you have to be very wary of implanting toric lenses when measurements may have been made in the presence of hypotony.

For example, I've seen instances in which keratometry done on an eye with a pressure of 0 mmHg showed what appeared to be 3 D of regular with-the-rule astigmatism; when the IOP was raised to a physiologic pressure, the astigmatism disappeared completely. If you'd placed a toric lens in this eye, you would have ended up actually inducing astigmatism after a more normal pressure was restored.

The bottom line is, if the eye has significant hypotony and you're starting from a very low IOP, I'd recommend addressing the hypotony first and performing cataract surgery later. You'll end up with much more accurate preoperative calculations and more predictable outcomes.

There will be situations in which the pressure is just a little low, and the patient doesn't have maculopathy or visual distortions. In that case I might decide to wait and address the low IOP during or after the cataract surgery, to avoid having to take the patient to the OR twice.

Correcting Low IOP

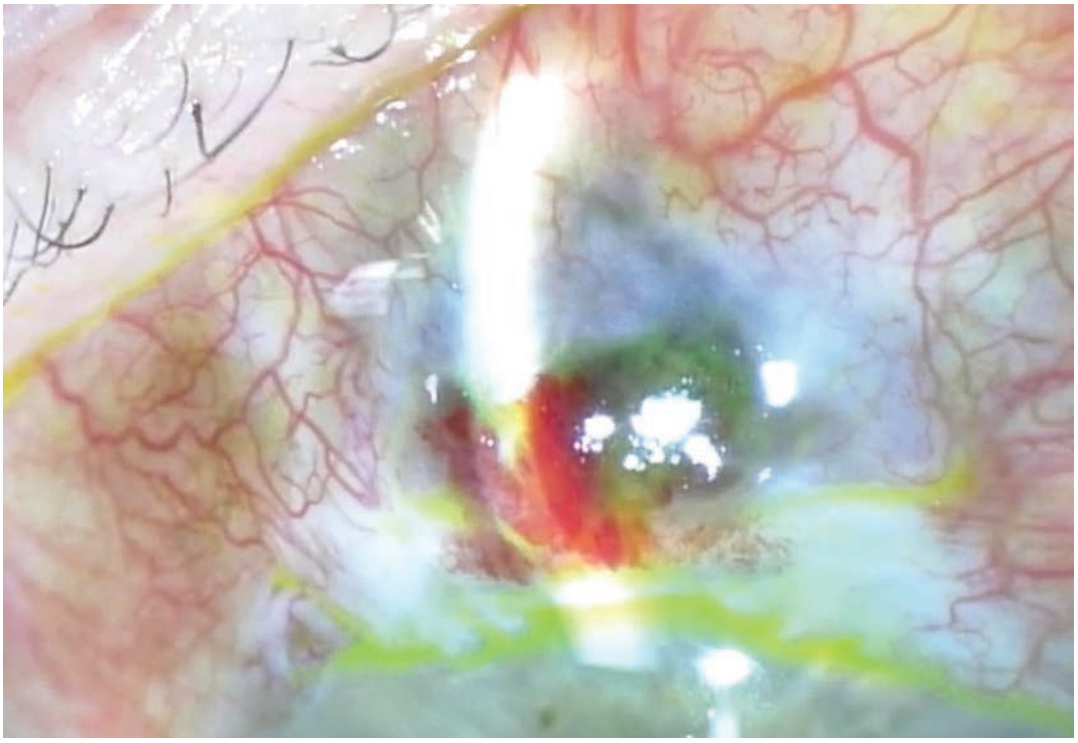
There are a number of techniques for addressing low IOP, but I've found three to be particularly helpful. The first is surgical revision of the trabeculectomy. This will give you the biggest increase in IOP, and this is the approach I'd typically recommend doing before cataract surgery. The second method is using fewer postoperative steroids following the cataract surgery. This is useful when you're just looking to nudge up the IOP. The third option I sometimes use is an autologous blood patch. It is easy to do in clinic and can help to raise the IOP a few points, and can be done either preoperatively or postoperatively, if cutting back on the steroids didn't quite raise the pressure enough.

Let's look at each of these more closely:

• ***Perform a surgical revision.*** This is useful if you're trying to increase the IOP by a significant margin. Often this involves replacing the nylon sutures in the scleral flap as a way to decrease the flow through the trabeculectomy flap. This has to be done in the OR and it takes time, both for the surgeon in the OR and for the patient through recovery. However, if you're starting from a point at which the patient is

significantly hypotonous and vision is symptomatic, this is the best route to go, even though it means an extra trip to the OR.

In terms of the benefits of choosing this option, it's the most effective way to increase the IOP. By decreasing the outflow through the trabeculectomy flap, you're getting to the root of the problem. The primary downside is that you could unintentionally trigger the original problem that caused the patient to need a trabeculectomy in the first place: too high a pressure. If the IOP climbs too high, you'll need to be prepared. Are you willing to do laser suture lysis? Bleb needling? Placing a tube shunt at some point in the future?



If the patient has a low IOP related to an overfiltering trabeculectomy, a blood patch can be used to elevate IOP a little. This involves injecting a little bit of the patient's blood into the bleb to promote conjunctival scarring and thus decrease aqueous outflow by a small amount.

This means that if you close off the trabeculectomy and decrease the flow, you have to be ready to deal with any unintended consequences. You have to be thinking about the next step, just in case you're too successful at getting the pressure back up.

One other caution: When you do this in the OR, do a more thorough conjunctival closure than you might do in an initial trabeculectomy surgery, because this eye's already been operated on, and the tissues may have already been exposed to mitomycin-C or other antimetabolites that can make the conjunctival tissue less robust.

Some patients will have a low pressure but be largely asymptomatic, so doing a surgical revision is probably not necessary. A patient like that might be on the edge of hypotony, but not yet in trouble. In that situation, it would make me feel better knowing that the intraocular pressure was a little bit higher, a little more physiologic, so I might use one of the next two techniques to nudge the IOP up just a little.

• ***Use fewer postoperative steroids.*** When doing a normal cataract surgery on a patient who doesn't have a trabeculectomy, my normal postoperative steroid regimen begins at four times a day, followed by a weekly taper. If a cataract patient has a well-functioning trabeculectomy, I revise this protocol. Studies have shown that performing cataract surgery on a patient with a trabeculectomy can cause the bleb profile to become smaller, and generally causes an IOP increase on the order of 2 to 4 mmHg.[1] Often, I'm looking to preserve flow through a trabeculectomy, so to help prevent the IOP rise, I increase the use of steroids, starting at every two hours.

In hypotony, I suggest taking advantage of this phenomenon instead. If the patient has just a small amount of hypotony—not enough to justify a trip to the OR for a flap revision—I'd complete a normal cataract surgery and then simply use fewer or no postoperative steroids. The idea is that the small amount of inflammation stirred up by the cataract surgery—if we don't temper it with steroids—may be enough to promote subconjunctival scarring. This can decrease the flow through the trabeculectomy, thus raising the IOP by a few points.

The biggest benefit of this approach is that it's very easy to do—you're simply using fewer or no postoperative drops following an otherwise normal cataract surgery. The downside is that you should only expect a small pressure increase. This strategy certainly won't cause the pressure to rebound from 0 mmHg, for example, but it's a really good technique if you're starting from 6 or 7 mmHg and just trying to get the IOP up by a small amount.

• ***Try using an autologous blood patch.*** The blood patch is another

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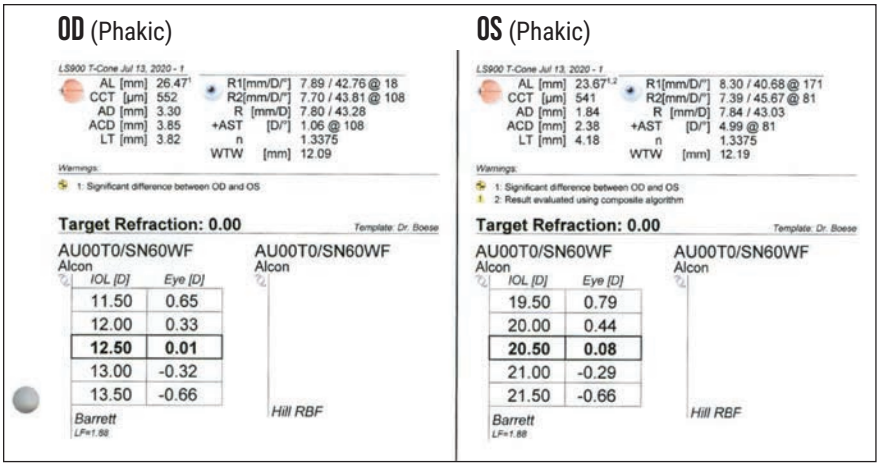

Intraocular lens calculations for a patient with hypotony in her left eye caused by a traumatic cyclodialysis cleft. Measurements found a nearly 3-mm difference in axial eye length between her eyes, resulting in an 8-D difference in IOL power.

option that only creates a small IOP increase; it involves injecting a little bit of the patient's blood into the bleb to promote conjunctival scarring and thus decrease outflow by a small amount.

The technique should be familiar to many surgeons; it's a lot like needling a bleb. We prep the eye much as we would for needling. Then, I have an assistant help draw up the patient's blood. The assistant immediately hands me a syringe containing a small amount of blood, and I add a 27- or 30-gauge needle. Starting away from the bleb, I tunnel underneath the conjunctiva and inject a little of the patient's blood into the bleb. (In needling, I'd be trying to break through the scarring and loculations; here I'm just trying to enter the bleb and loculations with as little disruption as possible.) It doesn't require much blood to achieve the desired effect.

This is not a novel technique, but it's certainly worth revisiting. It was first described in 1993 by James Wise, MD.[2] In his series, he found that doing this increased IOP from 5.5 to 8.2 mmHg, on average. Although this is a small increase, it's enough to improve visual acuity from average of 20/148 to 20/30, making a significant clinical difference for these patients. My experience has been similar.

Since this is done in clinic, you can use a blood patch to nudge up the pressure at any point. Also, you can use this in conjunction with the previous technique, in which you try to nudge the pressure up by using fewer postoperative steroids, if you didn't get enough effect.

The biggest advantage of this technique is that it's also very easy to do; it uses tools and techniques that a lot of us already have. The downside is that, like cutting back on the postoperative steroids, it will only give you a small IOP increase. So, you have to set appropriate expectations going in. You definitely can't use this to resolve hypotony starting at a pressure of 0 mmHg.

Intraoperative Considerations

Whenever I have a cataract surgery patient with a trabeculectomy, I recommend approaching the cataract surgery a little differently:

- ***Use a lower bottle height.*** The idea is to reduce the turbulence during the surgery. Excess flow can cause a subconjunctival donut, limiting visualization. It can also inadvertently land you in a position where the integrity of the bleb could be compromised, inviting an unexpected and complicated surgery to repair the damage.
- ***Take extra precautions to avoid nicking the conjunctiva when making your clear-cornea incision.*** You don't want to nick the conjunctival vessels, potentially causing a leak.

Interestingly, if the eye has a mature bleb, I don't find that the fluidics change much, even if the bleb is overfiltering. However, be wary of performing cataract surgery on an eye with a recently performed trabeculectomy; you may end up with a very unstable chamber.

Ensuring a Good Outcome

To summarize: When you're thinking about cataract surgery and the patient has an overfiltering trabeculectomy, there are a few different approaches that can be used, depending on the degree of hypotony. If the patient has clinical signs of hypotony, steps should be taken to raise the IOP before performing the IOL power calculations and cataract surgery. This will require two trips to the OR, but it's worth it; you're going to get better IOL power calculations, more controlled outcomes and happier patients.

On the other hand, if the patient has a low IOP with minimal or no hypotony, using fewer or no postoperative steroids after a standard phacoemulsification can cause decreased flow and increased IOP. If that isn't enough, then an autologous blood patch is a great clinical technique to augment the pressure.

No matter which approach you use, it's important to address hypotony to ensure the best possible outcome.

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How to Manage Pathologic Myopia

A look at the complications associated with the condition and the best ways to treat them.

RAZIYEH MAHMOUDZADEH, MD, SAMIR N. PATEL, MD, AND TAKU WAKABAYASHI, MD
PHILADELPHIA

The prevalence of myopia is increasing. Nearly half of the world's population is predicted to suffer from myopia by 2050, with 10 percent of the population being high myopes.[1] (High myopia is generally defined as a refractive error of more than -6 D or an axial length longer than 26 or 26.5 mm, although some studies define high myopia as a refractive error of at least -5 D.)[2,3] In addition to the obvious vision difficulties posed by myopia, high myopia can also be associated with the vision-threatening ocular structural changes of pathologic myopia. In this article, we'll detail the most effective way to diagnose and manage a patient with this condition.

Pathologic Myopia Overview

Pathologic myopia (myopic degeneration) is defined as the presence of structural changes in the posterior segment owing to an increased axial elongation.[4] Although the cut-off values of the refractive error and axial length aren't specified in the definition, pathologic myopia is usually associated with high myopia.

In the following sections, we'll delve into each of the vision-threatening conditions that are known to occur in eyes with pathologic myopia, including myopic choroidal neovascularization, myopic subretinal hemorrhage, myopic choroidal atrophy, dome-shaped macula, posterior staphyloma, myopic traction maculopathy and macular hole retinal detachment.

Myopic CNV

Myopic CNV is one of the most common vision-threatening complications in patients with pathologic myopia.[5] It affects 5 to 11 percent of patients with pathologic myopia and is bilateral in approximately 15 percent.[6] Patients with myopic CNV present with metamorphopsia (distortion of vision) and/or visual impairment similar to those with age-related macular degeneration. Ocular risk factors include lacquer cracks (fissures in the retinal pigment epithelium–Bruch's membrane–choriocapillaris complex), choroidal thinning, impaired choroidal circulation and patchy retinal atrophy in the posterior pole.[7] Incidence of myopic CNV is higher in eyes with lacquer cracks (29 percent) than in eyes with other types of myopic maculopathy.[8]

On examination, the CNV lesion often manifests as a light-colored

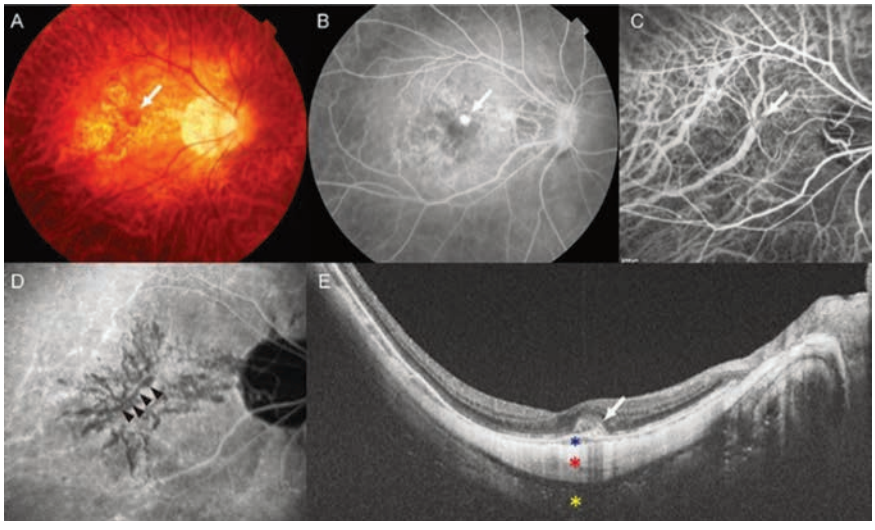

Figure 1. A 65-year-old female presented with a visual acuity of 20/30. The axial length was 29.5 mm. (A) Myopic choroidal neovascularization with hemorrhage (arrow). (B) Fluorescein angiography showing leakage (arrow). (C) Early-phase indocyanine green angiography revealing CNV (arrow). (D) Late-phase indocyanine angiography revealing lacquer cracks, a known risk factor for myopic CNV (arrows). (E) Swept-source optical coherence tomography shows a dome-shaped hyper-reflective lesion with subretinal fluid (white arrow). Asterisks indicate choroid (blue), sclera (red), and orbital fat (yellow).

This article has no commercial sponsorship.

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lesion with a dark, hyperpigmented rim, with or without subretinal hemorrhage, and sometimes exudates *(Figure 1)*. The diagnosis can be confirmed using several imaging techniques, including fluorescein angiography, indocyanine green angiography, spectral-domain optical coherence tomography, swept-source OCT and OCT angiography. Among these, FA conventionally has been the gold standard, particularly for the initial diagnosis of CNV. FA reveals hyperfluorescence in the early phase and dye leakage in the later phases, based on the CNV activity. However, because FA is an invasive diagnostic exam with potential side effects, SD-OCT is commonly used during follow-ups (or even for initial diagnosis) since it is a non-invasive technique for assessing the activity of the myopic CNV.

Active myopic CNV often reveals a dome-shaped hyperreflective elevation above the RPE, accompanied by subretinal fluid. When the activity of myopic CNV is uncertain, with minimal subretinal fluid on SD-OCT, SS-OCT may be helpful for the detection of very small CNV and subtle fluid *(Figure 2)*. SS-OCT uses longer wavelengths and can penetrate deeper into the posterior segment structures. A relatively thicker sclera and a thinner choroid are some biological indicators for myopic CNV on SS-OCT.[9] Early-phase ICGA provides information regarding choroidal circulation, and late-phase ICGA is useful for visualizing lacquer crack formation, which is responsible for the development of myopic CNV in many cases.[10]

OCTA is a non-invasive method of detecting myopic CNV, and is particularly useful in patients who are allergic to fluorescein dyes *(Figure 3)*. A recent study demonstrated that the acquisition rate of clear OCTA images in myopic CNV was as high as 76 percent.[11] The evaluation of the activity of myopic CNV with OCTA has also been attempted by assessing vascular branching and anastomoses of the CNV lesion.[11] However, evaluating the activity of the CNV lesion with OCTA alone is usually difficult because CNV lesions persist even after anti-vascular endothelial growth factor treatment.

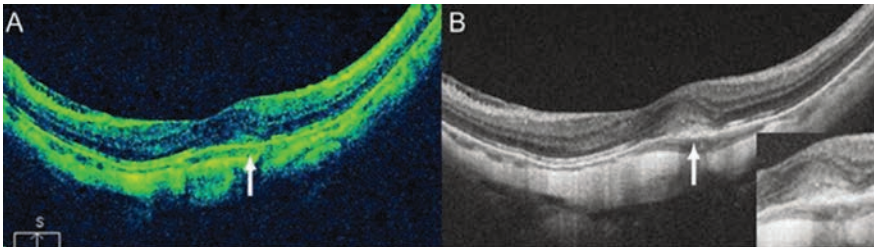

Figure 2. Although SD-OCT (A) is useful in detecting myopic CNV in most cases, SS-OCT (B) can more clearly detect CNV and subtle subretinal fluid, and better image the choroid.

The long-term outcome of myopic CNV is very poor if left untreated (visual acuity worsens to 20/200 or less within five years).[12] Intravitreal anti-VEGF injection is the current first-line treatment for myopic CNV.[5] Ranibizumab (Lucentis; Genentech) is the only FDA-approved medication; however, off-label use of bevacizumab has also been effective. Various clinical trials, such as MYRROR, RADIANCE, BRILLIANCE and SHINY, have demonstrated the safety and efficacy of anti-VEGF treatment for myopic CNV.[13] Early initiation of treatment is strongly recommended to achieve optimal outcomes.[14]

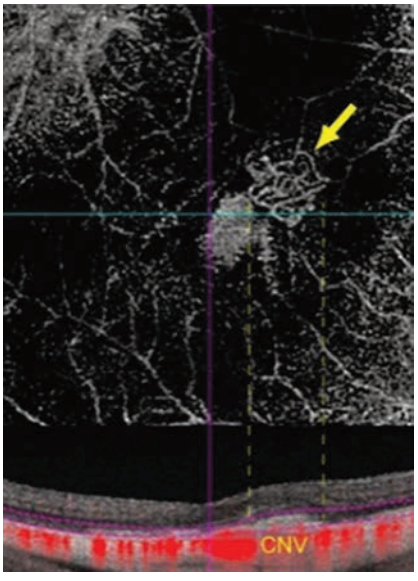

Figure 3. Non-invasive visualization of myopic CNV is possible with OCT angiography.

The treatment schedule will depend on disease activity. Compared to neovascular age-related macular degeneration, myopic CNV tends to regress more quickly, requiring fewer injections.[15,16] One study even showed that 67 percent of patients with myopic CNV (34/51 eyes) received just one injection during five years of follow-up.[17] However, some older patients may develop larger CNVs that resemble neovascular AMD, and may require multiple injections to achieve resolution.

The timing of and decision about retreatment for recurrent CNV can be challenging due to the subtlety of the imaging findings in myopic CNV. Visual impairment, subjective symptoms and OCT imaging should all be considered when evaluating for recurrences. Most recurrences occur within the first year following the onset of disease. A subsequent increase in the subfoveal choroidal thickness after an initial decrease following anti-VEGF therapy has been associated with a higher chance of CNV recurrence.[18]

Myopic Subretinal Hemorrhage

Myopic subretinal hemorrhage is often caused by lacquer crack formation in pathologic myopia.[19] It has a prevalence of nearly 3 percent in highly myopic eyes. Patients often present with symptoms similar to those of myopic CNV. On examination, subretinal hemorrhage is observed at the macula, similar to myopic CNV. However, FA shows blocked hypofluorescence, associ-

ated with hemorrhage, but without hyperfluorescent leakage *(Figure 4)*. SD-OCT may show subretinal fluid and projection of the hemorrhage within the retina, along with the Henle's fiber layer in some cases.[19] Late-phase ICGA is useful in visualizing the lacquer cracks; OCTA is useful for confirming the absence of myopic CNV.

The distinction between myopic CNV and hemorrhage from lacquer cracks is very important to make, because the treatment is different. Anti-VEGF treatment is not indicated in myopic subretinal hemorrhage without CNV. These patients have a more favorable visual prognosis than those with myopic CNV. Indeed, patients gradually recover vision without treatment, since the hemorrhage spontaneously resorbs. Some patients may have persistent visual impairment owing to damage to the photoreceptor cells caused by hemorrhage.[20] However, intervention is not required for this condition.

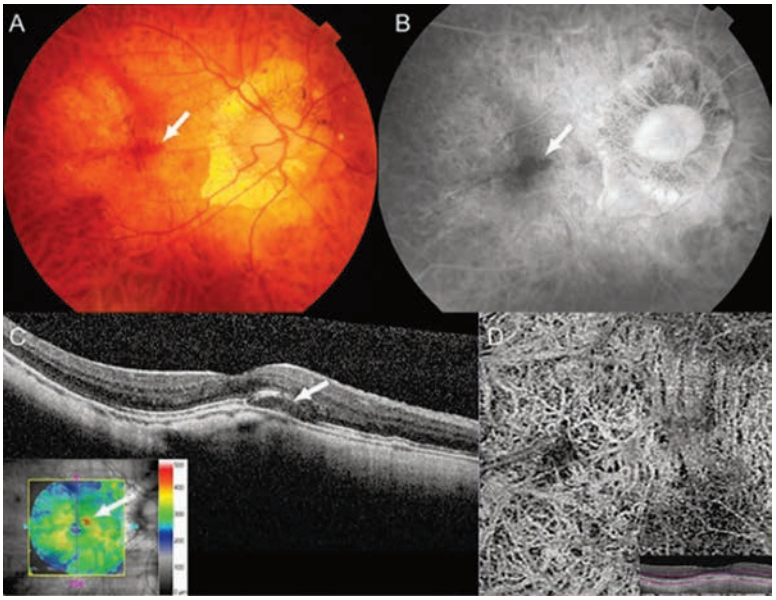

Figure 4. A 61-year-old female presented with blurred vision. (A) Fundus photograph showing submacular hemorrhage (white arrow). (B) Fluorescein angiography showing hypofluorescence associated with hemorrhage but without leakage (white arrow). (C) Swept-source optical coherence tomography (SS-OCT) showing elevation of the retina due to subretinal hemorrhage and fluid (white arrow). (D) OCT angiography shows an absence of myopic CNV.

Myopic Choroidal Atrophy

Chorioretinal atrophy is a common feature of pathological myopia. Atrophy is usually progressive, associated with age, axial length, myopic CNV and posterior staphyloma, and can occur in different patterns. The most recent classification (META-PM classification) categorizes myopic macular lesions into five categories: no myopic retinal lesions (category 0); tessellated fundus only (category 1); diffuse chorioretinal atrophy (category 2); patchy chorioretinal atrophy (category 3); and macular atrophy (category 4).[21] Three additional features—lacquer cracks, myopic CNV and Fuchs' spots—were added to these categories as "plus signs." Based on this classification, pathologic myopia is defined as equal to or greater than category 2, or the presence of a plus lesion or posterior staphyloma.

Myopic CNV is associated with further progression of chorioretinal atrophy *(Figure 5)*. Despite the stabilization of myopic CNV with anti-VEGF treatment, more than 90 percent of eyes experience a significant decline in vision during five to 10 years of follow-up, mainly owing to the development and progression of patchy retinal atrophy around regressed CNV tissue.[12] A study using SS-OCTA revealed that CNV-related macular atrophy wasn't simply chorioretinal atrophy but was an enlarged break in the Bruch's membrane around the myopic CNV.[21] Progressive chorioretinal atrophy could result in significant vision loss. Currently, no treatment exists for the slowing or recovery of chorioretinal atrophy, similar to atrophy following neovascular AMD. Since myopic chorioretinal atrophy is a leading cause of blindness in many countries, the development of a treatment is strongly desired.

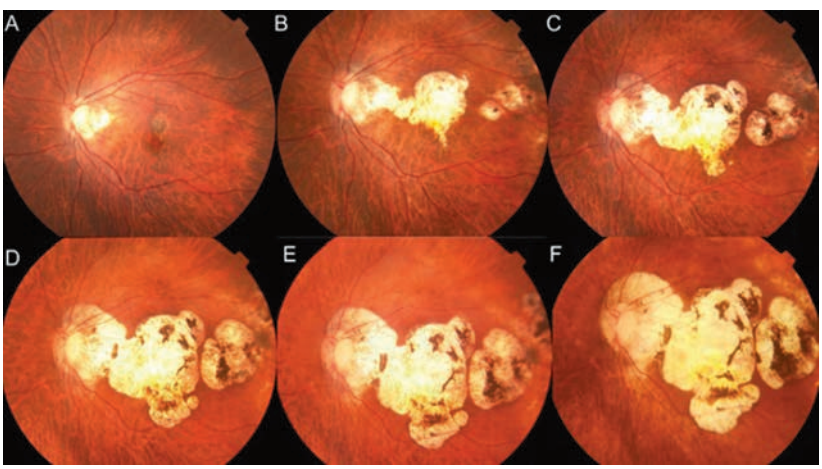

Figure 5. A 57-year-old female presented with myopic choroidal neovascularization. The axial length was 27.6 mm. During 20 years of follow-up, chorioretinal atrophy gradually progressed (A–F). Visual acuity decreased from 20/400 (A) to hand motions (F).

Dome-shaped Macula

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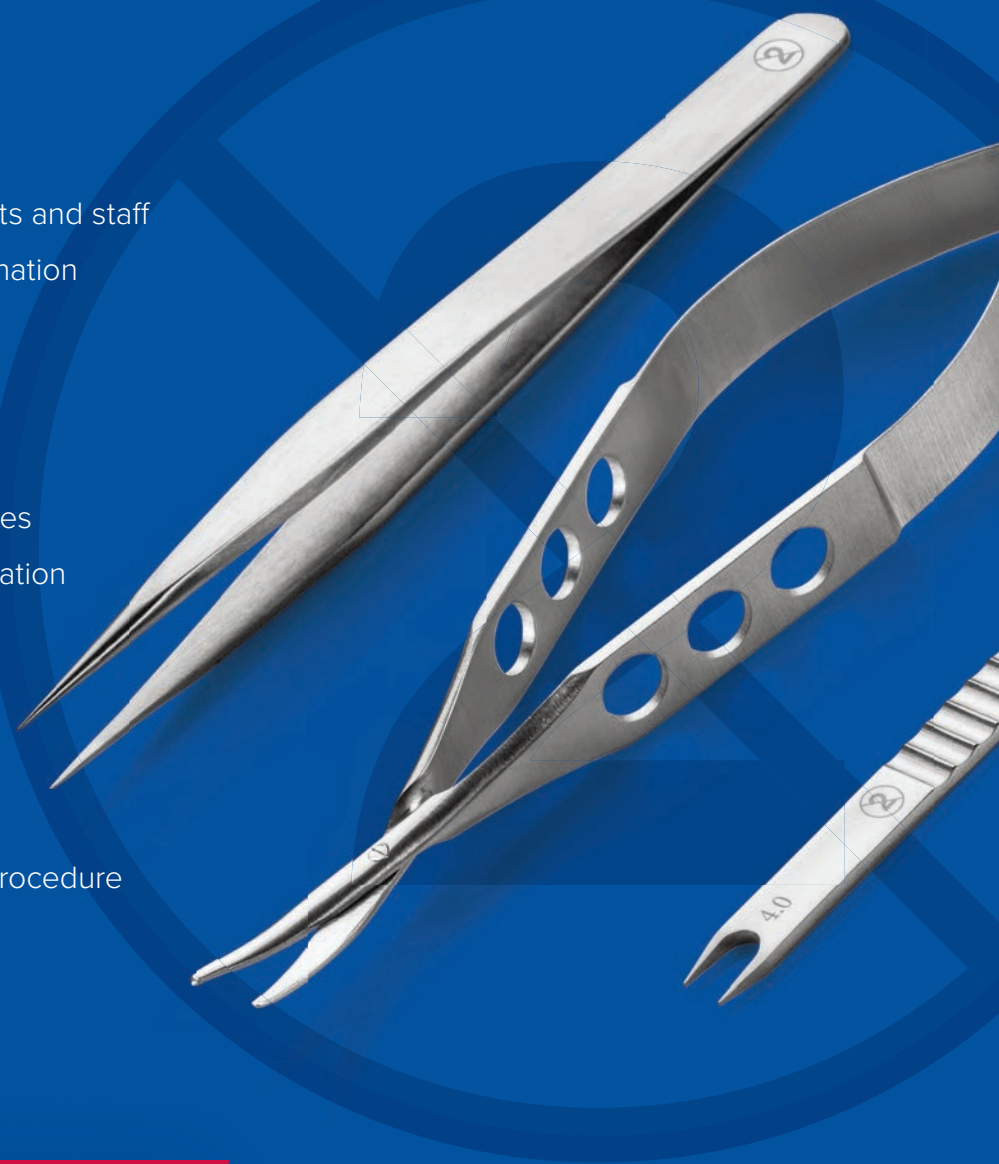

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the macula within the chorioretinal posterior concavity of the eye that's best visualized with OCT imaging *(Figure 6)*.[22] Three dimensional-magnetic resonance imaging (3D-MRI) has demonstrated morphological changes in the entire posterior pole, with a band-shaped inward convexity that extends horizontally from the optic disc through the fovea.[23] There are certain controversies regarding the choroidal thickness beneath the DSM. However, the central choroid seems to be thicker than the choroid in the surrounding staphyloma, and a relatively thicker sclera exists at the bulge apex.[24]

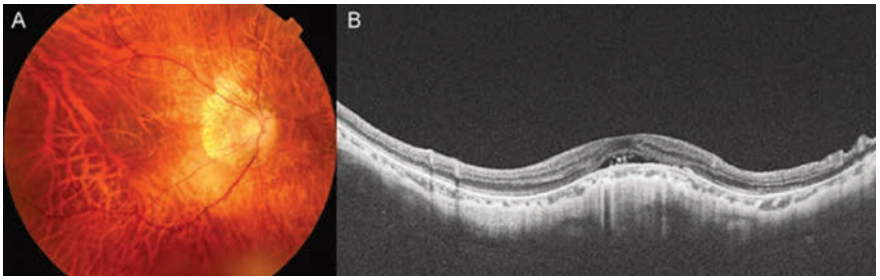

Figure 6. A case of dome-shaped macula. A 54-year-old female presented with visual acuity of 20/50. Swept-source optical coherence tomography shows subretinal fluid at the dome apex. This fluid is not from choroidal neovascular membranes, and doesn't respond to anti-VEGF treatment.

Isolated DSM can be associated with subretinal fluid, pigment epithelium detachment, CNV and polypoidal choroidal vasculopathy at the dome apex. Anti-VEGF isn't indicated for subretinal fluid from DSM alone, without CNV lesions. However, CNV or PCV should be promptly treated with anti-VEGF injections. The post-hoc analysis of the RADIANCE study (a randomized, controlled study of ranibizumab in patients with CNV secondary to pathologic myopia) confirmed that CNV with or without dome-shaped macula equally responds to anti-VEGF therapy, and the presence of dome-shaped macula doesn't alter the visual prognosis following ranibizumab treatment.[25]

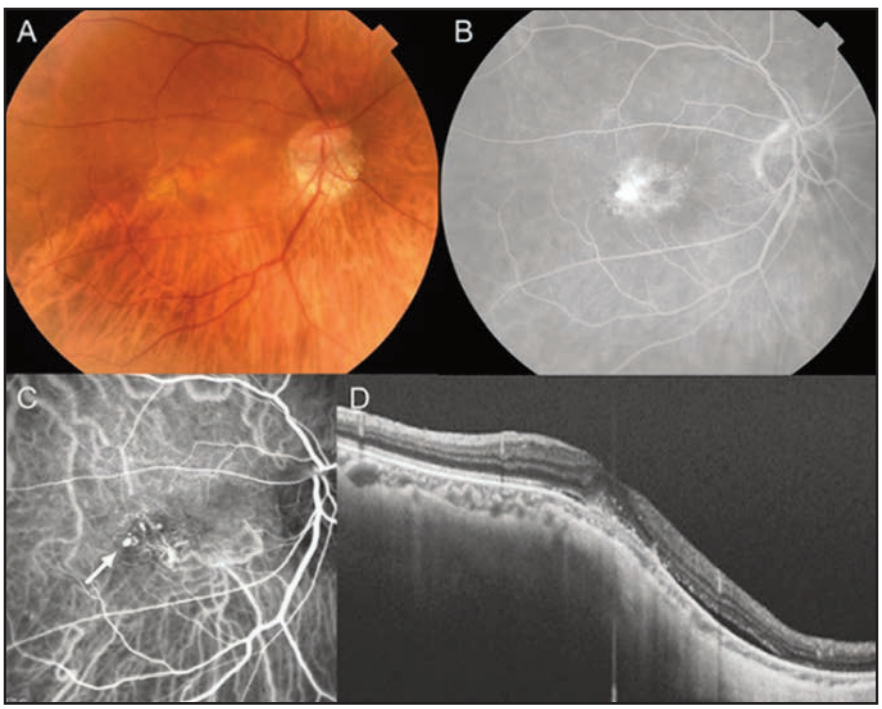

Figure 7. A 72-year-old female presented with visual acuity of 20/30. (A) Fundus photograph showing that the upper border of the inferior posterior staphyloma lies across the macula. (B) Fluorescein angiography showing leakage. (C) Indocyanine green angiography showing polypoidal choroidal vasculopathy in the macula (white arrow). (D) Swept-source optical coherence tomography showing shallow pigment epithelial detachment and subretinal fluid.

Posterior Staphyloma Issues

Posterior staphyloma is an outpouching of the eye wall with a radius of curvature less than the surrounding curvature of the eye, and it's a hallmark of pathologic myopia.[21] Nearly half of patients with pathologic myopia have staphylomas, and it's hypothesized that tissue loss and changes in the collagen fibrils cause scleral weakness. Posterior staphyloma was originally classified into 10 types; however, using 3D-MRI and widefield fundus imaging, it's recently been reclassified into six categories: the wide macular (most predominant type, 74 percent of the eyes with staphyloma); the narrow macular; peripapillary; nasal; inferior; and other configurations.[26] There's no widely accepted treatment for posterior staphyloma; however, scleral regeneration and scleral collagen cross-linking are being investigated.

Inferior posterior staphyloma is a subtype of posterior staphyloma and is commonly associated with tilted disc syndrome *(Figure 7)*. When the upper border of the inferior posterior staphyloma lies across the macula, macular complications may develop, resulting in visual impairment. Macular complications include macular atrophy, subretinal fluid, CNV and PCV. Similar to the treatment for complications associated with dome-shaped macula, CNV and PCV can be treated using anti-VEGF.[27]

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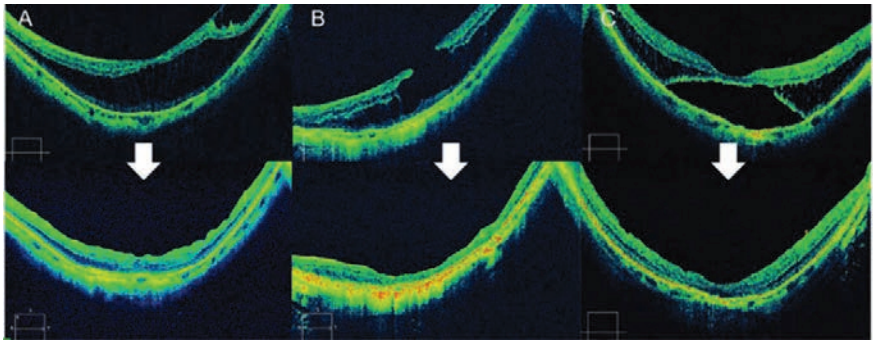

Figure 8. (A) Spectral-domain optical coherence tomography image showing myopic traction maculopathy (retinoschisis type) in a 65-year-old woman. Axial length was 28.1 mm, and visual acuity was 20/50. The MTM was resolved 12 months after surgery. Visual acuity improved to 20/30. (B) SD-OCT image showing MTM (lamellar macular hole type) in a 76-year-old woman. Axial length was 31.9 mm, and visual acuity was 20/60. The MTM resolved 12 months after surgery. Visual acuity remained stable. (C) SD-OCT image showing MTM (foveal detachment type) in a 76-year-old woman. The axial length was 27.3 mm, and visual acuity was 20/50. The MTM resolved 12 months after surgery. Visual acuity improved to 20/30.

Myopic Traction Maculopathy

Myopic traction maculopathy is characterized by retinal thickening, retinoschisis, lamellar macular hole formation and foveal detachment associated with high myopia *(Figure 8)*. Recently, ultra-widefield-SS-OCT revealed that MTM is present within the area of the staphylomas, and paravascular vitreal adhesions could play an important role in the development of MTM.[28,29] During its natural course, MTM could progress to a full-thickness macular hole and macular hole retinal detachment, owing to collective retinal traction from the adherent vitreous cortex, epiretinal membrane, internal limiting membrane, retinal vessels and posterior staphyloma.[30] Therefore, release of the retinal traction by pars plana vitrectomy with internal limiting peeling effectively resolves MTM and prevents macular hole and macular hole retinal detachment. However, postoperative macular hole opening could occur in 5 to 20 percent of the eyes following vitrectomy with ILM peeling, owing to the extremely thin fovea in MTM. The fovea-sparing ILM peeling technique is effective in preventing macular hole development.[31]

Early stages of MTM without foveal detachment are relatively stable and asymptomatic, and aren't indicated for surgery. However, surgical intervention is ideal before macular hole formation, so the best timing for surgery is gauged by changes in OCT imaging and when vision starts to become affected.

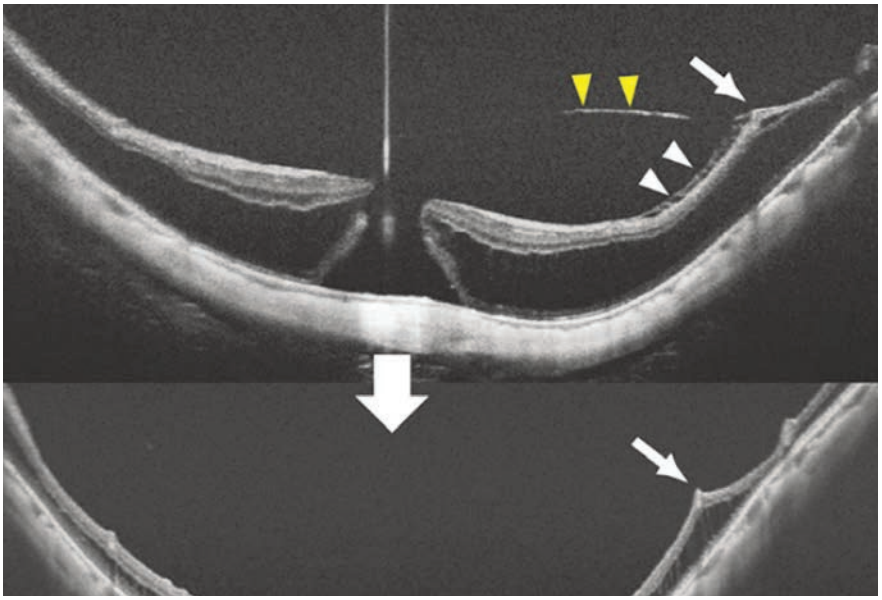

Figure 9. A 62-year-old female with a myopic macular hole and retinoschisis. The posterior staphyloma and traction from the vitreous cortex (yellow arrowheads), internal limiting membrane (ILM, white arrowheads), and blood vessels (white arrow) contribute to this condition. Vitrectomy and an inverted ILM flap resulted in hole closure.

Macular Hole Retinal Detachment

Macular hole and macular hole retinal detachment are serious complications associated with pathologic myopia *(Figure 9)*. The pathogenesis of macular hole involves vitreoretinal traction due to epiretinal membranes, remnants of the cortical vitreous, taut ILM and retinal vasculature adhesions. Axial elongation and posterior staphyloma contribute as well. This condition appears to be more common in Asian and female patients.[32]

Visual outcomes following vitrectomy for macular hole retinal detachment is usually poor (less than 20/200).[33] The macular hole closure rate is approximately 40 percent following standard ILM peeling for macular hole retinal detachment, but the inverted ILM flap technique increases the rate of hole closure.[34] Eliminating residual vitreous cortex and epiretinal membranes could decrease the likelihood of recurrent detachments. Macular buckling isn't widely performed, but studies have demonstrated its efficacy.[35]

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Other Complications

Glaucoma, cataract and rhegmatogenous retinal detachment occur more frequently in highly myopic eyes. Progressive axial length elongation has been reported in recent studies, even in adults,[36] which could further promote chorioretinal atrophy.

In conclusion, various complications may occur in patients with pathologic myopia that can result in visual impairment. Recent advances in multimodal imaging for diagnosis and medical/surgical treatment have significantly improved our knowledge of the disease phenotype. However, further advancements are needed to prevent and treat conditions such as posterior staphyloma, persistent elongation of the axial length, and consequent chorioretinal atrophy. Prevention of myopia itself is also particularly important in preventing vision loss resulting from pathologic myopia-related complications. ◀

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REVIEW of OPHTHALMOLOGY

Epithelial Ingrowth: Rare, But Manageable

After a first LASIK procedure, epithelial ingrowth is rare, but the rates go up after retreatment cases.

LINDA GROSS
SENIOR EDITOR

It doesn't happen as much anymore. When LASIK went mainstream in the 1990s, post-LASIK epithelial ingrowth rates were much higher in patients. The complication is characterized by the ingrowth of corneal epithelium at the interface between the flap and the stromal bed. Current prevalence rates range from 0 to 3.9 percent after primary LASIK, but can range from 10 to 20 percent after retreatment.[1] Here, refractive surgeons discuss today's approaches for epithelial ingrowth removal, and what considerations, if any, should be given to retreatment with LASIK in light of the higher ingrowth rates.

Do Nothing

"Epithelial ingrowth is very rare after primary LASIK," explains Andrew I. Caster, MD, FACS, medical director, Caster Eye Center Medical Group in Beverly Hills. "Yet, it's very common to have a little bit of peripheral epithelial ingrowth on a secondary flap-lift case. Frequently it only extends a millimeter from the edge, maybe two millimeters. In these cases, it really has no clinical impact.

"Therefore, if the epithelial ingrowth is peripheral and the refraction is very good, then I won't treat the epithelial ingrowth," Dr. Caster continues, adding that he'll schedule the patient for follow-up in a month or two. "I'll tell them to come back earlier if there are any problems, but most of the time it's asymptomatic and doesn't require treatment."

When Is It Cause for Concern?

"Epithelial ingrowth can be evident as soon as one week after a LASIK procedure but sometimes it doesn't appear for a month or more," explains Dr. Caster. "And sometimes there can be late-onset epithelial ingrowth, appearing six months to 12 months after a procedure, but that's rare."

So, when is ingrowth an issue? "Occasionally epithelial ingrowth will extend further in, and then it can have an effect on the refraction; lifts up the flap in that area and can cause astigmatism. That's what I would call clinically relevant epithelial ingrowth," warns Dr. Caster. "I find in my retreatment cases that it's around 10 percent overall. It's even more common when you're doing a hyperopic retreatment."

Epithelial ingrowth risk increases in retreatment candidates who had a mechanical keratectomy, which is associated with "a smaller optical zone and a smaller-sized flap," says Dr. Caster, adding that "the angle of the flap at the edge isn't very large. It's less perpendicular to the plane of the cornea, a common scenario with older keratomes."

LASIK done with a femtosecond laser has made a difference. "Flap surgery with a laser seems less likely to cause epithelial ingrowth because [flaps] have a more definitive edge to them and that may serve as a barrier to the incursion of epithelium at the interface of the flap," notes John Hovanesian, MD, in practice at Harvard Eye Associates in Laguna Hills, California. To help avoid ingrowth problems, procedure choice is also a factor. "The choice of what refractive procedure to use depends on surgeon preference, experience and the level of suspicion that the patient will have regrowth," he adds.

Another risk factor for epithelial ingrowth is eyelid conditions. "Conditions such as meibomian gland dysfunction, blepharitis, any external inflammation and dry eyes—all of those increase your risk of epithelial ingrowth after a LASIK flap lift retreatment," notes Dr. Caster.

Approaches to Ingrowth Removal

"The hardest part of the procedure is identifying the edge of the flap. Sometimes it can be hard to find," explains Dr. Caster, adding that indirect lighting can help. "If you bounce the light off of the iris or the limbus you get lighting throughout the cornea. That will illuminate the flap edge, which is hard to see with direct illumination." Another approach is to use the elbow of a Sinskey hook to put pressure on the cornea. "You'll see an indentation where the flap edge is." In rare cases, Dr. Caster says you can go into the OR and use the Sinskey hook to scrape away some of the epithelium "and the Sinskey hook will grab onto the edge of the flap,"

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.

but he cautions that this method can cause corneal abrasion.

Dr. Caster first identifies the edge of the flap. Then, once under the operating microscope, "I take a Sinskey hook and move it around all 270 degrees of the flap," he says. "You try not to drag epithelial cells underneath the flap, so as you move the Sinskey hook around, you pull up on it. Then I go in with a spatula and free up the entire flap, lifting it up and getting it out of the way."

However, Dr. Hovanesian says it's not always necessary to lift the entire flap. "Sometimes you can just lift it in the area of the ingrowth," he notes. "To remove the ingrowth, we typically scrape with a blunt spatula, although you can use a sharp blade, but at an obtuse angle so that you don't damage tissue." Essentially, he says, "The effort is to scrape away epithelium, both from the bed and from the backside of the flap, where we may have remnants of epithelium (*See Figure 1*). We try to remove epithelium from the site where it grows from underneath the edge of the flap. We'll often debride a little of the epithelium on the [corneal] surface as well, just to move it away from the edge of the flap and lessen the chance that it will find its way back down."

"A lot of times the epithelium is very soft, and you can just use some dry Weck-Cel (BVI) sponges to wipe it away. Otherwise you can use a hockey-stick-shaped instrument to free up the epithelial cells," says Dr. Caster. He wipes it all off and then goes back with a dry sponge to get any epithelium hanging over the edge. If there's a lot of epithelium, he'll go to the underside of the flap and scrape it with a sponge or a hockey-stick instrument.

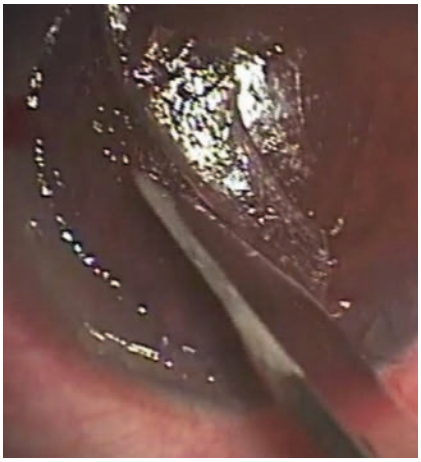

Figure 1. Dr. Hovanesian uses a no.15 blade to scrape epithelium from underneath the flap interface.

"In recalcitrant cases I will remove the ingrowth and then glue and suture the flap down," says Dr. Hovanesian. (*See Figure 2*) "The idea is to close the conduit. The glue fills that space for a few days and maybe retards the advancement of the epithelium. The idea is that two stromal surfaces will close a little more completely, preventing epithelium from reentering the previously opened door."

Dr. Caster says he doesn't remove a thin rim around the edge of the epithelium. "We want to seal this thing back down without the epithelium growing underneath," he explains. "You want to accomplish your goal with the minimum amount of manipulation to avoid swelling." He doesn't use sutures or glue. "I've not had to resort to suturing the end of flaps or other more aggressive treatments," he remarks. "This simple way of removing epithelial ingrowth has worked in my hands."

Others have investigated approaches that don't require lifting the flap. Dr. Hovanesian recalls the work of Jorge L. Alio, MD, from Alicante, Spain, who's published on his experience with the YAG laser method, which uses low-energy laser bursts targeted toward the flap interface to induce scarring to shrink the space between the flap and the bed.[3]

Risk and Retreatment Considerations

Refractive surgeons who are risk-averse to epithelial ingrowth may alter their retreatment plans. "A lot of surgeons follow the one-year rule," notes Dr. Hovanesian. "If it's after one year, they don't lift a flap because of concerns about epithelial ingrowth."

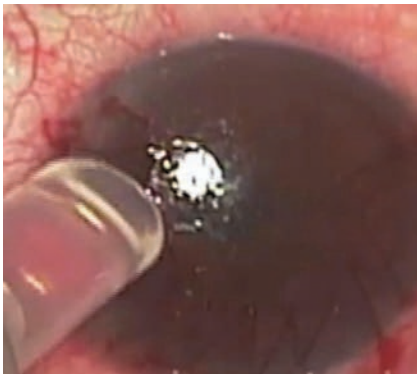

Figure 2. In this same procedure, Dr. Hovanesian has already sutured down the flap, and is applying the thrombin component of fibrin tissue adhesive to the ocular surface. The full procedure can be viewed at https://youtu.be/fW-iuWZCQeM

Dr. Caster describes his approach: "If I'm doing a hyperopic retreatment, I explain to patients that the risk of epithelial ingrowth could be higher than 10 percent," he says. "And I present the alternative, which is to do a PRK." Although he typically prefers LASIK, Dr. Caster says, "If I were going to do a large hyperopic retreatment where the initial flap was done with an older mechanical keratome, I might lean towards the PRK."

Ideally, it comes down to eliminating the need for retreatments. "We lived through some challenging times in the early days of LASIK," recalls Dr Hovanesian. "But we've been refining techniques, laser platforms have improved, and now we're seeing very high rates of accuracy. We don't do as many enhancements, so because enhancements have gone down, epithelial ingrowth has gone down." ◀

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PRODUCT REVIEW

New items on the market to improve clinical care and strengthen your practice.

RETINAL THERAPY

Refillable Anti-VEGF Port Delivery System Approved

In October, the FDA approved Genentech's port-delivery system with ranibizumab, now called Susvimo (ranibizumab injection) 100 mg/mL, for intravitreal use via ocular implant for the treatment of neovascular age-related macular degeneration that's previously responded to at least two anti-vascular endothelial growth factor (VEGF) injections.

Genentech says that Susvimo is the only FDA-approved treatment for wet AMD that offers as few as two treatments per year. Susvimo is a refillable, permanent eye implant that continuously releases a customized formulation of ranibizumab to the eye. The implant is surgically inserted into the eye during a one-time, outpatient procedure and refilled every six months.

The approval is based on the results of the Phase III Archway study, which the company says showed wet AMD patients treated with Susvimo achieved vision gains equivalent to monthly ranibizumab injections through 40 weeks of treatment. For more information, visit gene.com.

Xipere is Here

Also in October, the FDA approved Xipere, (triamcinolone acetonide injectable suspension) Bausch + Lomb/Clearside Biomedical's suprachoroidal injection for the treatment of uveitic macular edema. Xipere is the first drug to use the suprachoroidal space, which the company says provides targeted delivery and compartmentalization of medication. To deliver the drug to the suprachoroidal space, the physician uses the proprietary SCS Microinjector, which was developed by Clearside.

The FDA approval of Xipere was based on results from PEACHTREE, a randomized, multicenter, double-masked, sham-controlled Phase III clinical trial of 160 patients with macular edema associated with uveitis. The primary efficacy endpoint was improvement in best-corrected vision by at least 15 letters from baseline after 24 weeks. The drug's maker says that, in the trial, a statistically significantly greater proportion of patients treated with Xipere (47 percent) achieved at least a 15-letter improvement in BCVA than patients in the control arm (16 percent, $p<0.01$) at Week 24.

The company says the drug will be available for sale in the first quarter of 2022. For information, visit bausch.com.

OCULAR SURFACE

Follow Your Nose to Dry-eye Relief

Applying topical eye drops has long been a mainstay of treating dry-eye disease, but patient noncompliance and the potential for ocular irritation can challenge patients. An alternative approach using nasal stimulation of the trigeminal parasympathetic pathway now is possible with a unique repurposing of the pharmaceutical agent varenicline, which is also used in the smoking-cessation drug Chantix. The new nasally-administered dry-eye treatment, called Tyrvaya (varenicline solution 0.03 mg) from Oyster Point Pharma, recently received FDA approval.

Tyrvaya, a cholinergic agonist, triggers basal tear production, the company explains. After four weeks of b.i.d. administration, about half of patients using the treatment demonstrated 10 mm or more improvement in Schirmer's scores, according to a company statement. The most common patient complaint was sneezing, reported in 82 percent of the study participants.

The spray will be available by prescription beginning in November, Oyster Point says. For more information, visit oysterpointrx.com.

PEDIATRIC OPHTHALMOLOGY

New Amblyopia Therapy Approved

Luminopia says its new software, Luminopia One, is the first FDA approved digital therapeutic for children with amblyopia—and the first for any neuro-visual disorder. The software is designed for use with compatible head-mounted displays, and is indicated for children aged 4 to 7 with amblyopia associated with anisometropia and/or mild strabismus who are receiving treatment instruction by a trained eye-care professional. The company says Luminopia One allows kids to watch therapeutically modified versions of their favorite TV shows and movies with a virtual reality headset to improve their vision by training the eyes to work together. The therapy is prescribed for use at home for one hour per day, six days a week, for 12-week periods. For more information, visit luminopia.com.

IMAGING AND TESTING

Eidon Offers a Wider View

The Eidon ultra-widefield lens is the newest module in

iCare's confocal retinal imaging platform. The lens module captures 120-degree images of a patient's retina in one shot, or up to 200-degree images with its mosaic function, the company says. iCare says the high optical resolution enables clinicians to detect small details and signs of pathology from the center to the periphery. The module can also be retrofitted to most Eidon fundus imaging systems, the company adds, allowing capture of ultra-widefield infrared, autofluorescence and fluorescein angiography images.
For information, visit icare-world.com/uwfl.

Front-to-back Assessment of Pathologies

A new multi-modal device can perform various assessments that may help you detect early signs of cataracts, glaucoma, retinal and corneal pathologies, the manufacturer suggests. The Visionix VX650 from Luneau Technology brings together into one device the abilities of the following equipment: autorefractor; keratometer; aberrometer; topographer; pachymeter; Scheimpflug camera; tonometer; and 45-degree fundus camera, according to a company press release.

Capturing such data with a single device reduces patient movement through the practice, improving convenience and workflow efficiency, Luneau suggests, by allowing for ocular health screenings to be done in the pre-test room. For more information, visit luneautechusa.com.

A New Player In Electrophysiology Testing

The MonPackOne Vision Monitor, a visual function analysis platform, was recently approved by the FDA for vision electrophysiology testing.

Metrovision says the system can perform dark adaptometry, full-field stimulus threshold testing, pupillometry and vision electrophysiology testing such as ganzfeld flash electroretinography (ERG) and visual-evoked potential (VEP), pattern ERG and VEP, multifocal ERG and VEP and sensory electro-oculography. Additionally, the company says that MonPackOne is the only commercially available instrument that performs both dark- and light-adapted full-field perimetry. For information, call +1 (716) 352-2009.

Keep Your Distance, Get Your Data

An autophoropter, the Vision-S 700 refraction station, recently launched by Essilor Instruments, allows for remotely controlled testing, requiring no physical contact between you and the patient from start to finish, says the company.

The new device uses a unique "liquid lens" optical module and software algorithms that allow simultaneous and continuous variations of lens power by automatically compensating for any change in sphere, cylinder and axis. Essilor says this feature cuts time from the refraction process—potentially down to three minutes—without sacrificing accuracy. For more information, visit essilorinstrumentsusa.com. ◀

EDITED BY RAKHI MELVANI, MD
WILLS EYE RESIDENT CASE REPORT

A 47-year-old man presents for an evaluation of a sensation of fullness in his left eye.

THEODORE BOWE, MD, AND ROBERT B. PENNE, MD
PHILADELPHIA

Presentation and Initial Work-up

A 47-year-old man presented to Wills Eye Oculoplastic Department for a second opinion and evaluation of fullness of the left eye. He reported that he had an outpatient computed tomography scan and magnetic resonance imaging scan *(Figure 1)* which were notable for a "large left orbital mass, primarily intraconal with extraconal extension superiorly and laterally, concerning for a benign, slow-flow venous malformation."

Upon initial ocular examination the patient had a visual acuity of 20/30 by pinhole in the right eye and 20/20 in the left eye. No afferent pupillary defect was noted. Confrontational visual fields were full. Decreased abduction of the left eye was noted, with subjective diplopia in left gaze. Intraocular pressures were 18 mmHg in both eyes. Hertel measurements showed 5 mm of proptosis of the left eye. There was noted to be some resistance to retropulsion in the left eye, with superotemporal fullness. On dilated fundus exam he was noted to have choroidal folds in the left eye. He was referred to neurosurgery at Jefferson for consideration of embolization of the left vascular orbital mass.

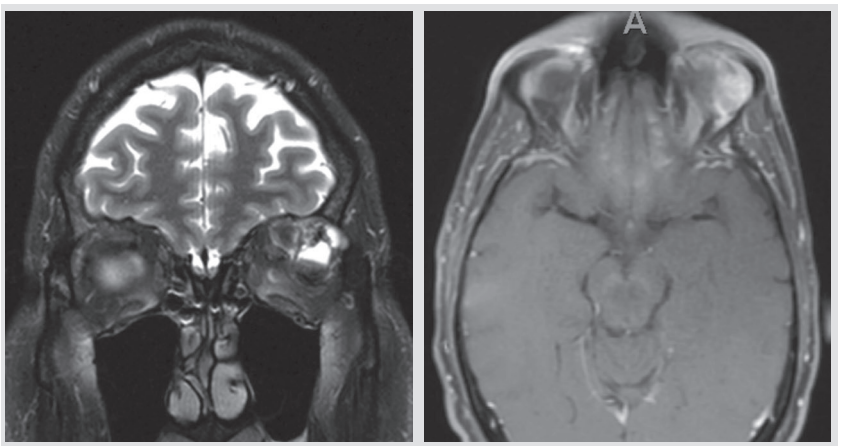

Figure 1. Outside imaging center MRI images with left orbital mass, read as, "lobulated with enhancement of septations. A small vascular channel is seen … The most common lesion of this nature in this area is a slow-flow venous malformation. Other vascular lesions are not excluded."

Due to the COVID-19 pandemic, the patient was initially seen by neurosurgery via a telemedicine appointment. At the time of his neurosurgical follow up, the patient reported no blurry vision, double vision, pain or other visual/ocular symptoms, other than intermittent fullness in the left eye. The patient was scheduled for a diagnostic cerebral angiogram to determine whether this was a high-flow vascular lesion and whether he would be a good candidate for embolization. This was notable for no obvious vascular lesions within the orbit, confirming no high flow to the lesion. In consultation, ophthalmology and neurosurgery determined that direct puncture onyx embolization followed by orbitotomy was indicated.

Medical History

The patient denied any past ocular history. Past medical history included testosterone supplementation for low testosterone levels. Family history included myocardial infarction on his paternal side and an unknown cancer on his maternal side. Social history was significant for tobacco use for a few decades, though the patient had quit seven years prior to presentation. Current medications included testosterone and vitamin D.

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

Best regards,
Zaina Al-Mohtaseb, MD, Derek DelMonte, MD and Jonathan Rubenstein, MD

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Exam

On postoperative day zero of his embolization, ocular examination demonstrated visual acuity of 20/20 in the right eye and 20/70 in the left eye. Pupils were noted to be 3 mm in dark/2 mm in light in the right eye and 4 mm in dark/3 mm in light in the left eye. There was no frank APD. Intraocular pressures were 14 and 22 mmHg in the right and left eyes, respectively. Extraocular motility was full in the right eye, with -0.5 adduction, -1 abduction, and -2 supraduction in the left. Moderate left upper lid edema and mild left lower lid edema were noted.

What is your diagnosis? What further work-up would you pursue? The diagnosis appears below.

Work-up, Diagnosis and Treatment

Oculoplastics proceeded with left orbitotomy under general anesthesia the following day. Intraoperatively, the lesion was found to be multiloculated, with many pockets of white cloudy fluid and other pockets of thick white toothpaste-like material. These pockets also contained onyx. The lesion didn't appear to be avascular intraoperatively. The mass displaced the globe medially, inferiorly and anteriorly, with additional displacement of the left superior and lateral rectus muscles. The lesion was adherent to the lateral rectus, optic nerve and globe, and was impossible to resect completely. Partial mass resection and biopsy were completed.

Biopsy of the lesion resulted in a pathologic diagnosis of invasive, high-grade adenocarcinoma of the left lacrimal gland. Molecular evaluation revealed it was estrogen receptor negative, progesterone receptor negative, HER2 Neu positive. The patient was referred to medical oncology. His adenocarcinoma was found to strongly express the androgen receptor and his testosterone supplementation was discontinued. There was no evidence of metastatic disease. Otolaryngology performed a sentinel lymph node biopsy, which was negative. Repeat MRI, as expected, showed the mass to be smaller, but there was still residual disease in the orbit (*Figure 2*). The patient underwent left orbital exenteration and adjuvant radiation therapy.

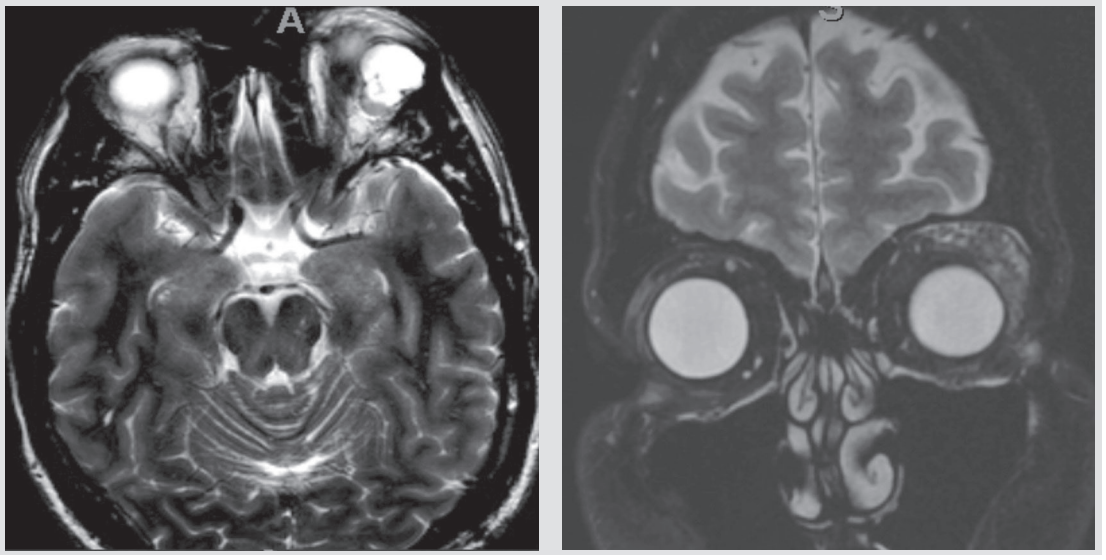

Figure 2. Two MRI images demonstrating recurrent/residual disease in the left orbit months after the initial left orbitotomy.

Discussion

Primary ductal adenocarcinoma of the lacrimal gland is a rare malignancy that was first reported in 1996.[1] The literature on ductal adenocarcinoma of the lacrimal gland is largely composed of case reports and reviews. Dr. Steffen Heegaard of the University of Copenhagen published a review and several case reports in 2017 in *Acta Ophthalmologica*, which described a 4:1 male-to-female predominance of patients in the literature, with a median age of 64 years at diagnosis.[2]

The most typical presenting symptoms have been reported to be proptosis and restriction of eye movements, with or without diplopia.[3] Radiographically, it can present as a lobulated mass on CT. On MRI, they

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have been reported to appear similarl to salivary duct carcinomas, which have been described as having low signaling intensity on T-2 weighted images, ill-defined borders and invasion into surrounding structures.[4,5] These ambiguous radiographical findings, along with the disease's rarity, can lead to initial diagnostic uncertainty, as was the case for our patient.

While the literature on this rare primary malignancy is scarce, management and treatment decisions have been assisted by the pathological and molecular similarities to ductal carcinomas of the salivary gland and the breast. These neoplasms all originate from the epithelial lining of glandular ducts. Salivary duct carcinoma has been noted to be particularly histologically and genotypically similar to lacrimal duct adenocarcinoma.[2,3,6] The demographics of salivary ductal carcinoma patients in the literature are also similar to those of lacrimal ductal adenocarcinoma, with a male predominance (71 percent) and a median age of onset of 66.[7]

While the literature on this rare primary malignancy is scarce, management and treatment decisions have been assisted by the pathological and molecular similarities to ductal carcinomas of the salivary gland and the breast.

The mainstay treatment of lacrimal gland ductal adenocarcinoma is staging followed by local resection, with consideration of adjuvant radiation therapy. Presentation with metastatic disease is reportedly unusual, only representing five percent of cases.[2] However, eventual development of metastatic disease is not uncommon, with one recent literature review finding 58 percent of patients eventually had metastatic lesions.[3] Another review found that half of patients presenting without metastasis that continued to follow up developed distant metastasis, and 41 percent of patients died of their disease.[2]

In addition to phenotypic and histological similarities to salivary duct carcinoma, there are genetic commonalities. Both neoplasms frequently have an amplification of human epidermal growth factor 2 (HER2).[8,9] This amplification can be targeted by a monoclonal antibody, trastuzumab. This treatment results in survival benefit in HER2-positive ductal carcinoma of the breast. However, there is insufficient data on the use of trastuzumab in HER2-positive salivary duct carcinoma or lacrimal gland adenocarcinoma, and the limited data that's been collected has not showed a significant effect on HER2-positive salivary duct carcinomas.[10] Very limited data has showed that androgen deprivation therapy might be beneficial for patients with widely metastatic or recurrent disease.[3]

In conclusion, primary lacrimal ductal adenocarcinoma is a rare malignancy that typically presents with unilateral proptosis and limitation of extraocular movements. Primary lacrimal ductal adenocarcinomas appear to have a predilection for older men. They're not typically metastatic at the time of presentation, but many patients develop distant metastasis and eventually die of their disease. Due to the rarity of this malignancy, treatment decisions are often informed by the phenotypic and genotypic similarities to salivary gland (and breast) carcinoma. Surgical resection followed by adjuvant radiotherapy is the mainstay of treatment, with exenteration often being necessary. Other treatment modalities, including adjuvant chemotherapy, adjuvant radiation, and/or therapies targeting specific mutations, are dependent on the presence or absence of metastasis, positron-emission tomography/computed tomography findings and histopathologic/genotypic findings. ◀

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