REVIEW® of Ophthalmology

November 2020

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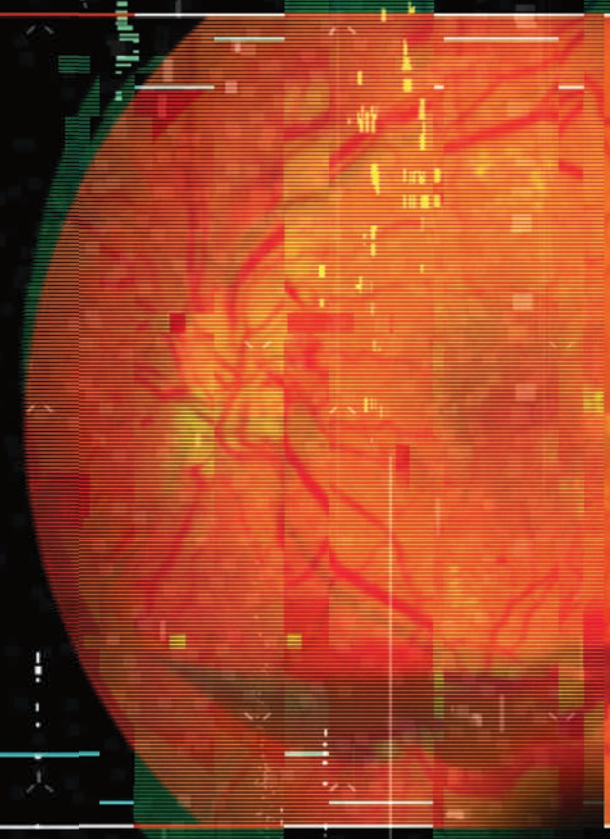

OPHTHALMOLOGISTS IN THE MACHINE: THE AI ERA

Experts discuss the upsides and downsides of AI and the new FDA-approved AI systems. *P. 38*

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INDICATIONS

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IMPORTANT SAFETY INFORMATION

Ulcerative keratitis can occur. Patients should be monitored for resolution of epithelial defects.

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

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

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

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

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

MA-01953A

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REVIEW NEWS
Volume XXVII • No. 11 • November 2020

An Update on Medicare Cuts to Surgical Reimbursement

This has been an unprecedented year. Practices across the country have lost nearly a quarter of the year's revenue due to the COVID-19 public health emergency, among other hardships. There is, however, another hurdle to face: CMS has finalized a policy that will cut reimbursement for surgical specialties, effective January 2021.

Under the proposed change, all E/M services will increase in value, and the conversion factor will decrease, in order to maintain budget neutrality. This will result in payment decreases for all other codes in the physician fee schedule, including postop visits.

Wilmer Eye Institute's Michael Repka, MD, the AAO's medical director for governmental affairs, says that surgery-heavy ophthalmic subspecialties will experience the most negative effects from these changes, as will those who don't perform much E/M.

"In almost every surgical code, there are postop visits included," he explains. "If you have a 10-day global period, you might have one postop visit, or if you have a 90-day global period, you might have three postop visits. Those have traditionally been valued at the same level as E/M service, so if you were to have a level-three visit within the postop period, you'd receive the work RVU payment and that payment would be based on the level-three E/M service. CMS has decided not to increase the work RVUs of each of these postop visits, so they won't get the same increase that the E/M visits get.

"All surgical or procedural specialties will be affected," he continues. "They're going to get lower payments for level-three services than for free-standing E/M services, which are done in the office. This policy change is important because as much as a third of the value of surgery is in the postop visits. Not only do we have the conversion factor going down due to the E/M increases, but we're also not getting the work value increases relative for the postop visits.

"A reduction of this magnitude in a normal year may be devastating," he adds, "but following 2020, which has been a bad year, this may not allow practices the room to recover in 2021. That being said, Congress and HHS were incredibly quick in the spring and early summer with relief aid, and we're very grateful for that action. It could have been much worse."

The Academy, along with the American College of Surgeons, ASCRS and other groups, has launched a lobbying effort called the Surgical Care Coalition. It aims to tell policymakers why these changes are potentially harmful to surgical access. The Coalition asks for the following:

1. Waive budget neutrality.
2. Eliminate the add-on complexity code.
3. Value postop and E/M visits equally.

"It's great that the E/M codes are paying more—they really needed to do that," Dr. Repka says. "If budget neutrality is waived, all other code values will stay the same and E/M can increase. That's five billion dollars; the add-on complexity code also affects the conversion factor and comes to about 1.8 billion dollars. Valuing postop visits equally to E/M visits will be a more equitable solution than the double hit CMS has proposed. However, all this requires payment and money.

"The final rule is due out—we're told—in early December, which is about 30 days later than normal," he continues. "This is a problem for our members because these changes have to be incorporated by EMRs, practice management software, EMR companies and insurance companies. There are always changes from CMS to incorporate every year to prepare the new fee schedule and other rules for January 1st, but this year we'll have less than half the time we usually do. Rushing often leads to errors, and those could take months to fix."

Dr. Repka says that despite ongoing legislative efforts, it's very likely this policy change in some form will go into effect—but that doesn't mean there's nothing you can do. He recommends examining the new E/M descriptors to see where it's advantageous to code outpatient visits with an E/M code, rather than with an Eye code.

"The E/M descriptors become very different in 2021," he says. "You'll choose your code level based entirely on medical decision-making. That includes the number of diagnoses you consider for the problem, the number of problems you manage, the amount of laboratory testing that has to be ordered and incorporated, the number of records that need to be reviewed

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References: 1. Ngo W, Srinivasan S, Houtman D, Jones L. The relief of dry eye signs and symptoms using a combination of lubricants, lid hygiene and ocular nutraceuticals. *J Optom.* 2017 Jan-Mar;10(1):26-33. 2. Jones L, Downie L, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* Jul 2017;15:575-628.

and the risk of morbidity from the problems you're managing. Taking a little time to learn the new codes, and particularly the steps in medical decision-making, will help you make the most advantageous choice."

In addition, he recommends looking at the MPFS and your expenses. "Be sure that you'll still be able to care for certain conditions," he says. "Also keep tabs on what's being published by medical organizations and CMS. There will be many rules changes. It may also be a good idea to take a course on how to code under the new evaluation-and-management system." REVIEW

Case Report: What's Behind the Mask?

Iva R. Kalita, MD, Harsh Vardhan Singh, MD, and K. Veena, MD
Pondicherry, India

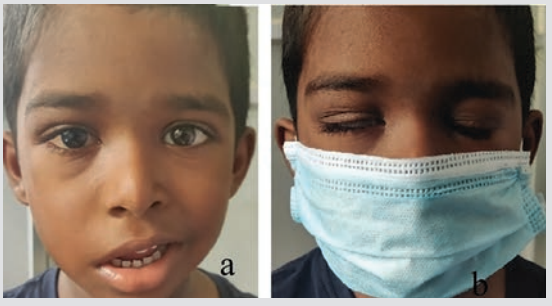
Wearing personal protective equipment, both for patients and providers, is inevitable in the time of COVID. However, it's important not to let our aversion to infection prevent us from observing the whole patient and allow us to miss a key sign or symptom, as the following pediatric ophthalmology case demonstrates.

The Patient Presents

A 10-year-old boy was brought to our pediatric ophthalmology department by his father. The patient complained of redness in his right eye for two days *(Figure 1)*. On slit lamp examination, the conjunctiva was congested, though the rest of the anterior segment was normal. We made a diagnosis of conjunctivitis.

It's important to note that eliciting a history and symptoms from a pediatric patient can be very different than getting the information from an adult; in most cases, questioning the parent will provide the pertinent information. Indeed, upon repeated requests for any other symptoms, the father added that the child had not eaten solid food for the past two days. This revelation compelled us to remove the mask and examine the patient further. What we observed surprised us: The child had right facial palsy with lagophthalmos. *(Figures 2a and 2b)* Fortunately, before the child could be chalked up as just another case of acute conjunctivitis, looking behind the mask tipped us off to more serious signs.

We feel that this incident is important, as it can serve to make every clinician aware that they may miss ominous signs if they don't temporarily remove a patient's protective mask to look behind it, even during these tense, germaphobic times. The chances of missing clinical signs are increased when half the patient's face is covered, or if the clinician is seeing him or her via a tele-ophthalmology consult. It pays to remain vigilant.



Top: The patient presented with signs of conjunctival congestion OD, leading to a snap diagnosis of conjunctivitis. Bottom (a and b): Removing the mask, however, revealed right-sided mouth deviation and lagophthalmos, suggestive of lower motor neuron facial palsy.

Dr. Kalita is a Fellow in the Department of Pediatric Ophthalmology and Strabismus at Aravind Eye Hospital in Pondicherry. Dr. Vardhan Singh is a Fellow in the Department of Retina-Vitreous at Aravind Eye Hospital. Dr. Veena is the head of the Department of Pediatric Ophthalmology and Strabismus at Aravind Eye Hospital.

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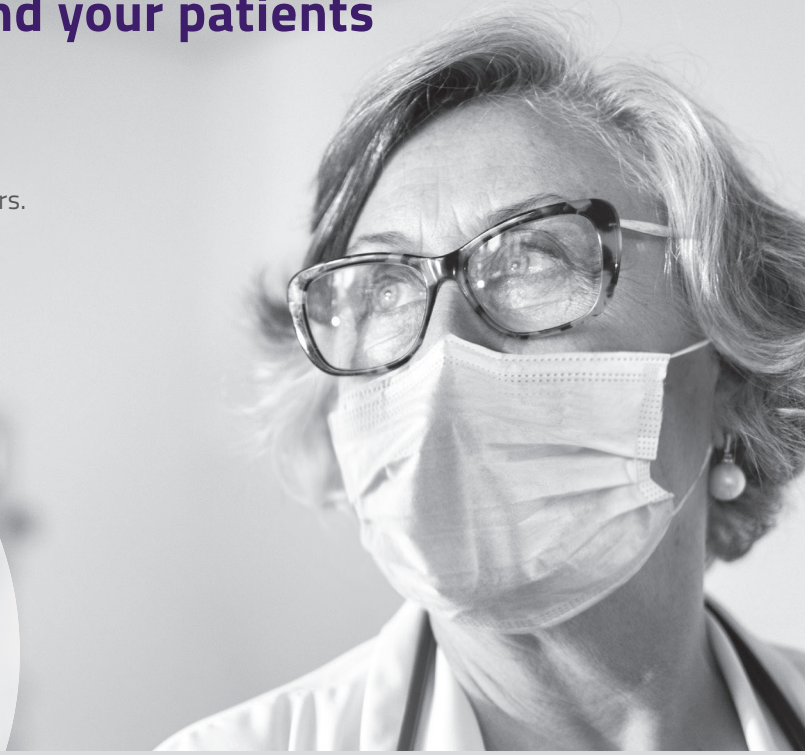

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INDICATION AND USAGE

DEXYCU® (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

- Prolonged use of corticosteroids, including DEXYCU, may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision
- Steroids should be used with caution in the presence of glaucoma

Delayed Healing

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids

Exacerbation of Infection

- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures

WARNINGS AND PRECAUTIONS (cont'd)

Exacerbation of Infection (cont'd)

- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and 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
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection

Cataract Progression

- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts

ADVERSE REACTIONS

- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis

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

EyePoint PHARMACEUTICALS

07/2020
US-DEX-2000095

DEXYCU (dexamethasone intraocular suspension) 9%,
for intraocular administration
Initial U.S. Approval: 1958

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

1 INDICATIONS AND USAGE

DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

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

5.2 Delayed Healing

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

5.3 Exacerbation of Infection

The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection.

5.4 Cataract Progression

The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Increase in Intraocular Pressure *[see Warnings and Precautions (5.1)]*
- Delayed Healing *[see Warnings and Precautions (5.2)]*
- Infection Exacerbation *[see Warnings and Precautions (5.3)]*
- Cataract Progression *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

The following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively *[see Data in the full prescribing information].*

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use

Safety and effectiveness of DEXYCU in pediatric patients have not been established.

8.5 Geriatric Use

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

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472

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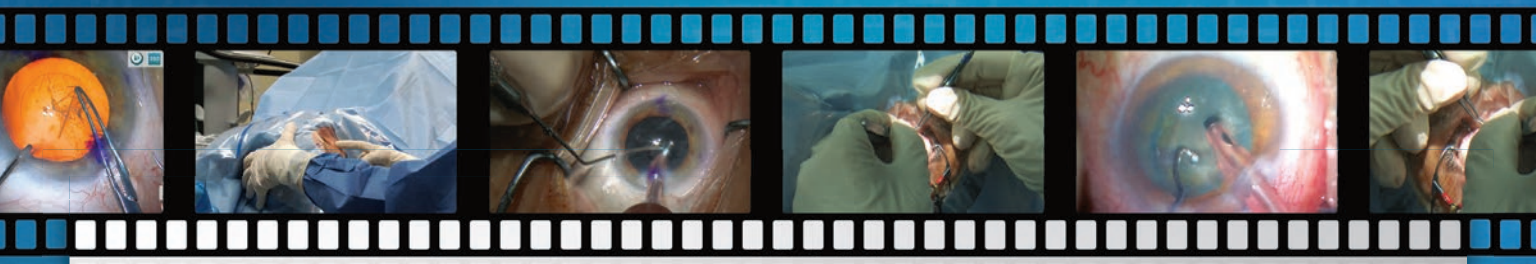

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Episode 59:
"Mature White Cataract: the importance of anterior capsule morphology"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
Phacoemulsification of a mature, white cataract is performed. The morphology of the anterior capsule (flat vs convex) and its impact on the capsulorhexis procedure are discussed.

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Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical techniques using a variety of instrumentation and settings.

This educational activity aims to present a series of Dr. Mackool's surgical videos, carefully selected to address the specific learning objectives of this activity, with the goal of making surgical training available as needed online for surgeons motivated to improve or expand their surgical repertoire.

Learning Objective

After completion of this educational activity, participants should be able to:

- promote awareness of anterior capsule morphology and its effect on successful performance of the capsulorhexis.

Satisfactory Completion - Learners must pass a post-test and complete an evaluation form to receive a certificate of completion. You must listen to/view the entire video as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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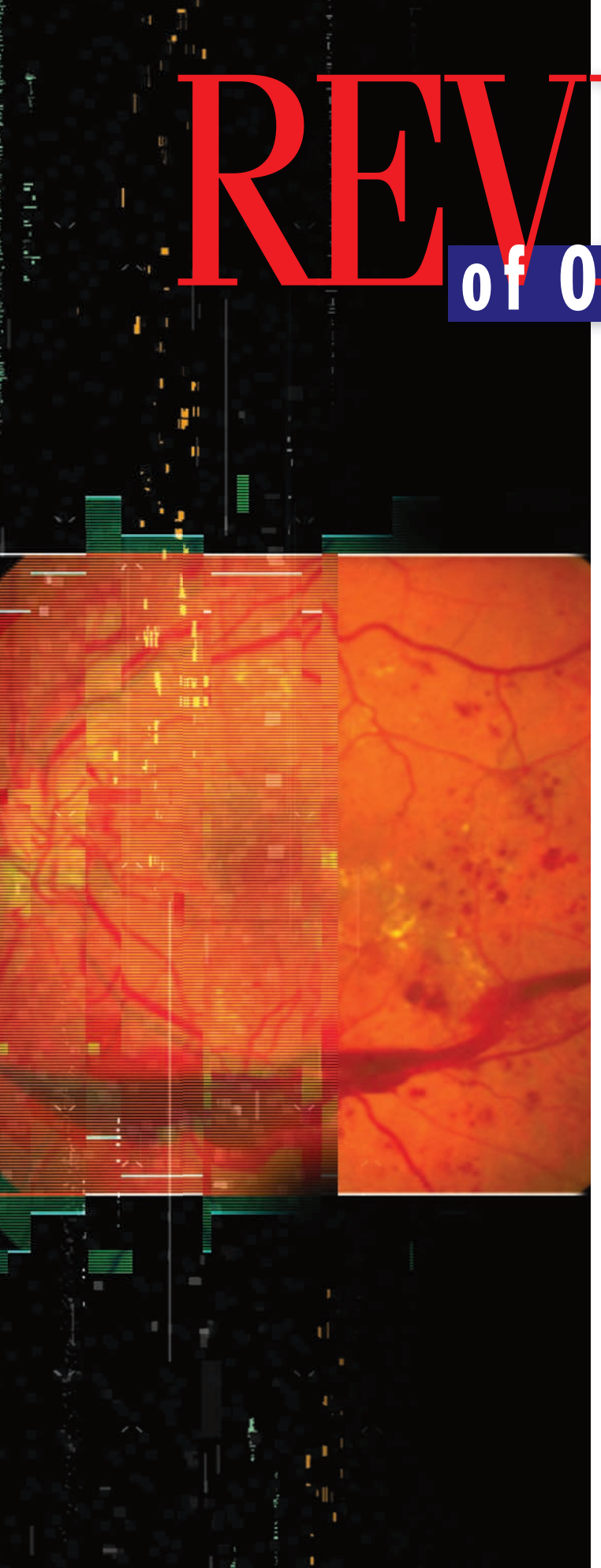

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REVIEW® of Ophthalmology

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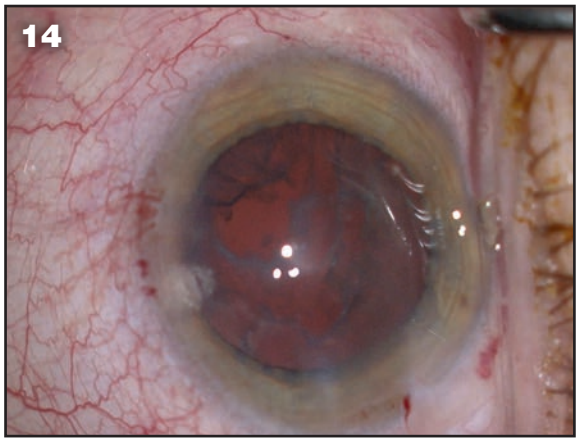
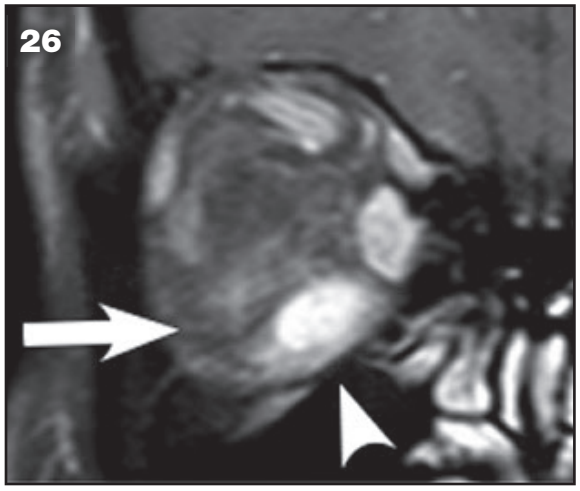
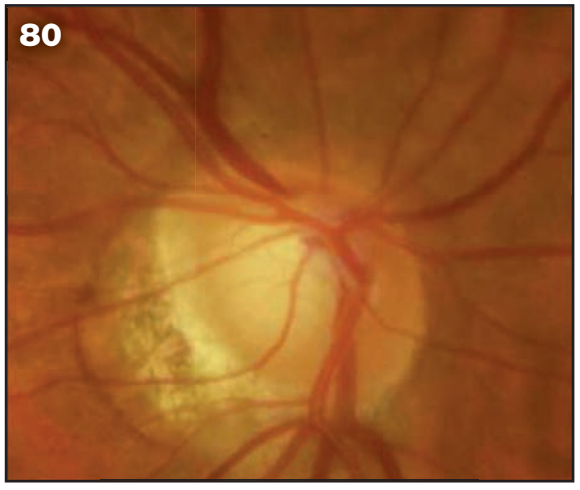
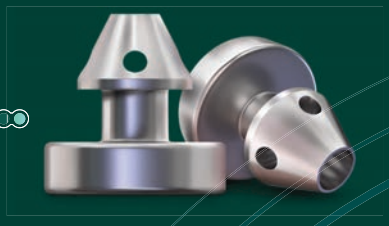






INTRODUCING

iStent *inject*® W



EVOLVING DESIGN. ADVANCING PREDICTABILITY.

Featuring a wide flange at its base, the new precision engineered iStent *inject*® W is designed to:

- Safely and effectively control your patient's glaucoma[1]
- Optimize stent visualization while maintaining a truly micro-scale footprint
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- Deliver procedural predictability

Don't miss the opportunity to make a once-in-a-lifetime difference for your cataract patients with mild-to-moderate glaucoma.

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REFERENCE:
1. Samuelson TW, Sarkisian SR, Lubeck DM, et al. Prospective, randomized, controlled pivotal trial of an ab interno implanted trabecular micro-bypass in primary open-angle glaucoma and cataract. *Ophthalmology.* Jun 2019;126(6):811-821.

INDICATION FOR USE. The iStent *inject*® W Trabecular Micro-Bypass System Model G2-W is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma. **CONTRAINDICATIONS**. The iStent *inject* W is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent *inject* W is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent *inject* W have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents. **ADVERSE EVENTS.** Common postoperative adverse events reported in the iStent *inject*® randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent *inject* vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

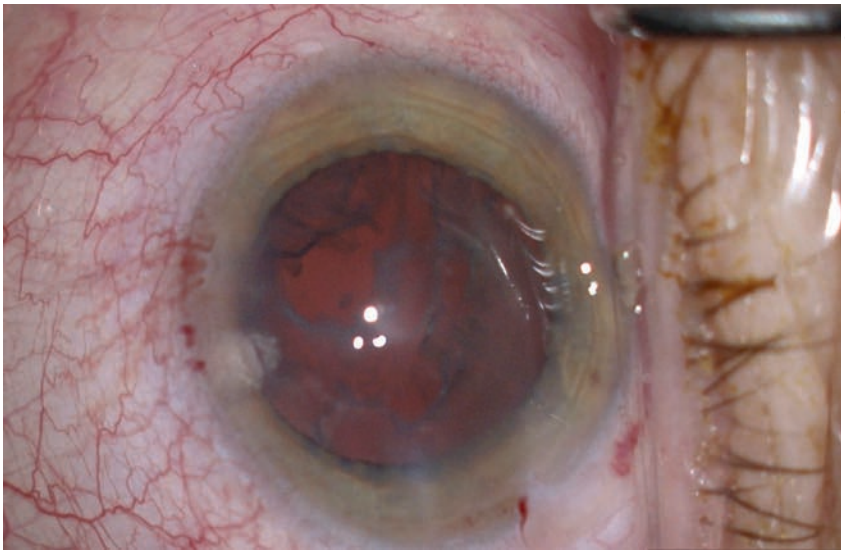
GLAUKOS®

Managing Posterior Capsule Ruptures

How to anticipate and manage a mid-surgery episode, complete the surgery effectively and ensure proper follow-up.

Sean McKinney, Senior Editor

Even some of the most successful cataract surgeons admit to an occasional posterior capsule rupture, a rare complication that can send even the most routine surgery on a tense and perilous 15-to-30-minute rescue mission. Experts in this article share insights about the best approaches. Find out the best ways to assess risk, respond confidently, complete surgery successfully and decide when to refer patients for retina follow-up.



Douglas K. Grayson, MD

Figure 1. Posterior capsule tear with nucleus and cortex still present.

Assessing Risk Factors

Surgeons say the first step to preparing for a posterior capsule rupture is understanding how one of these events can develop. Douglas K. Grayson, MD, of Omni Eye Services, which has multiple offices in the New Jersey-New York City area, points to causes and risk factors that range from the well-known to the less obvious. Like other surgeons, he cites two of the most common: posterior polar cataracts and dense lenses.

"It could also be a surgeon's technical error," he notes. "In addition, you could encounter a cataract that's adherent to the posterior capsule, preventing you from removing it without causing a tear in an area of weakness in the posterior capsule."

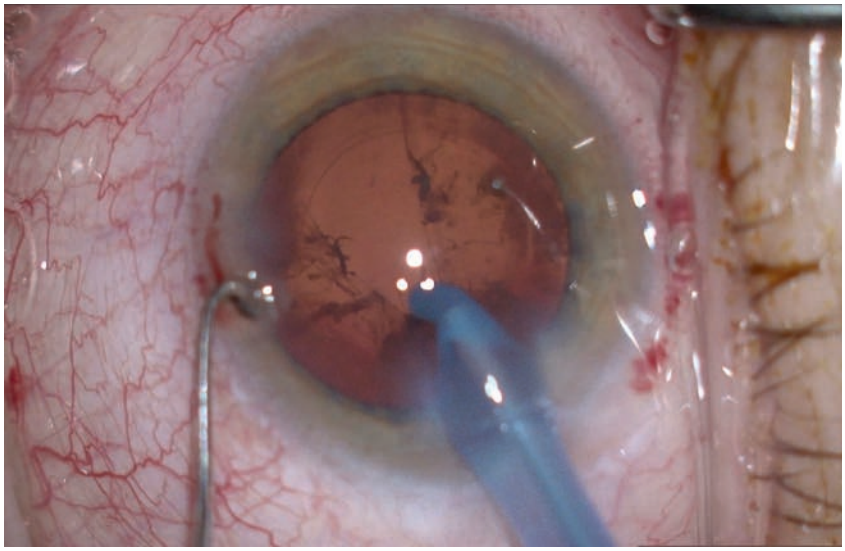
A posterior chamber rupture can also take you by surprise when you're operating on a patient who has been treated for retinal disease, he points out. "What's not realized is that when retinal patients receive Avastin, Lucentis, Eylea and steroid injections, retinal specialists can sometimes nick the posterior capsule," he observes. "That will cause a small, focal weakening of the posterior capsule, which won't be manifest until you go in with a phaco probe under infusion. You can't even see that developing and, as a result, you'll have a higher rate of posterior lens dislocation."

Small pupil size, poor dilation, a history of preoperative trauma and poor patient cooperation can also increase risks, according to R. Bruce Wallace III, MD, FACS, founder

and medical director of Wallace Eye Surgery in Alexandria, Louisiana, and clinical professor of ophthalmology at Louisiana State University and Tulane Schools of Medicine in New Orleans. "If a patient is moving around, even with anesthesia, that alone may be the reason for the tear," he says. "I also pay attention to significant increases in posterior vitreous pressure. You want to work on a nice, soft eye, but it can suddenly have an increase in pressure that can bulge the posterior capsule and vitreous forward."

Zaina Al-Mohtaseb, MD, associate professor and associate residency program director at Baylor College of Medicine in Houston, always has a higher level of concern with patients who have undergone prior retina surgery or have diseases such as pseudoexfoliation. "All cataract surgeons will have complications, and I have definitely had posterior capsule ruptures," she says. "But I firmly believe that you should be prepared for possible complications and have everything you need, even though you won't have to use those instruments most of the time. This is especially important when operating on patients at risk for complications such as a posterior capsule rupture and anterior vitrectomy.

Zonulopathy can also be associated with a history of trauma or mature cataract, adds Bryan S. Lee, MD, JD, in private practice at Altos Eye Physicians in Los Altos, California, and an adjunct clinical assistant professor of ophthalmology at Stanford University. "I do quite a few patients who are post-vitrectomy and those patients are more prone to have zonulopathy," says Dr. Lee. "Sometimes, I know in advance that a patient is at higher risk of capsular break and that's kind of easier to deal with. Even though I'm obviously trying to do everything I can to avoid a vitrectomy, if I need to do one because of a really bad cataract, I think, 'Well, okay, I kind of knew this might happen.' I can talk about it preop with the patient and be able to schedule accordingly, blocking off additional time in the operating room and letting the OR staff know that this could be a complicated case."



Douglas K. Grayson, MD

Figure 2. Cortical removal with a posterior capsular tear.

In general, however, surgeons point out that risks factors for a ruptured posterior capsule are often not apparent. You need to be prepared for known and unknown co-morbidities that increase the risk of capsular rupture, zonular loss and unplanned vitrectomy, which can occur during any cataract procedure.

After Sudden Ruptures

One common concern surgeons share is that they won't respond properly if a posterior capsule ruptures during a case that's expected to be straightforward. Dr. Al-Mohtaseb, who supervises residents at Houston's Ben Taub Hospital, says she's seen residents fail to even *notice* a posterior capsule rupture. "This can lead to much worse complications," she says. "For example, if a surgeon doesn't see vitreous and continues to phaco, that can result in retinal tears and detachments from traction on the vitreous."

The second-worst response, she adds, is to become so stressed that you panic and suddenly remove all of your instruments from the eye. "Doing this flattens the chamber and causes more complications," she points out. "Your best response is to remain calm and put OVD in the eye before removing the phaco probe. Then take a moment to set up the correct instrumentation for vitrectomy and use Triesence or Kenalog (triamcinolone, Bristol-Myers Squibb) to stain the vitreous. These cases can still go well. Your goal should be to try to avoid another surgery by not losing the lens or lens fragments posteriorly or by putting traction on the vitreous."

In such cases, Dr. Lee agrees that panic can easily emerge as your arch-enemy. "Of course, arresting panic is easier said than done," he admits, describing a sudden stream of worries that can flood his mind and disrupt a calm and measured response. "You start thinking about a lot of things at once: 'I'm going to have to discuss this with the patient. Am I going to be able to put a lens in this patient? I want to do the right thing but I may

FIRST AND ONLY
FDA-APPROVED TREATMENT FOR THYROID EYE DISEASE

IT'S TIME FOR A BREAKTHROUGH
IT'S TIME FOR TEPEZZA

TEPEZZA is proven to[1-4]:

- **Decrease proptosis[1]**
- **Improve diplopia[1]**
- **Reduce orbital pain, redness, and swelling[2,3]**
- **Improve functional vision and patient appearance[2,3]**

...in patients with Thyroid Eye Disease (TED), without concomitant steroids (vs placebo at Week 24).[2-4]

Learn more at TEDbreakthrough.com

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

References: 1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon. **2.** Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341-352. **3.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761. **4.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18)(suppl):1748-1761. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1614949/suppl_file/nejmoa1614949_appendix.pdf.

TEPEZZA™
teprotumumab-trbw

Significantly greater proptosis responder rate* (Study 2)[1,2]

TEPEZZA **83%** **TEPEZZA (n=41)**

vs

Placebo **10%** **Placebo (n=42)**

P<0.001 at Week 24

*Both the safety and efficacy of TEPEZZA were evaluated in 2 randomized, double-masked, placebo-controlled clinical trials (Studies 1 and 2) consisting of 171 patients with TED (84 were randomized to TEPEZZA and 87 to placebo). The primary endpoint in Studies 1 and 2 was proptosis responder rate, defined as having a ≥2-mm reduction from baseline in proptosis in the study eye at Week 24 without deterioration (≥2-mm increase in proptosis) in the non-study eye.[1]

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be managed with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

Please see Brief Summary of Prescribing Information for TEPEZZA on following page.

HORIZON

TEPEZZA™
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions [see Warnings and Precautions]
- Exacerbation of Inflammatory Bowel Disease [see Warnings and Precautions]
- Hyperglycemia [see Warnings and Precautions]

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 safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase
c - Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor-1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There is insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss [see Data]. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA.

If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breastfed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations). Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.

Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-Related Reactions

Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Inflammatory Bowel Disease

Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia

Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control medications as appropriate. Encourage compliance with glycemic control.

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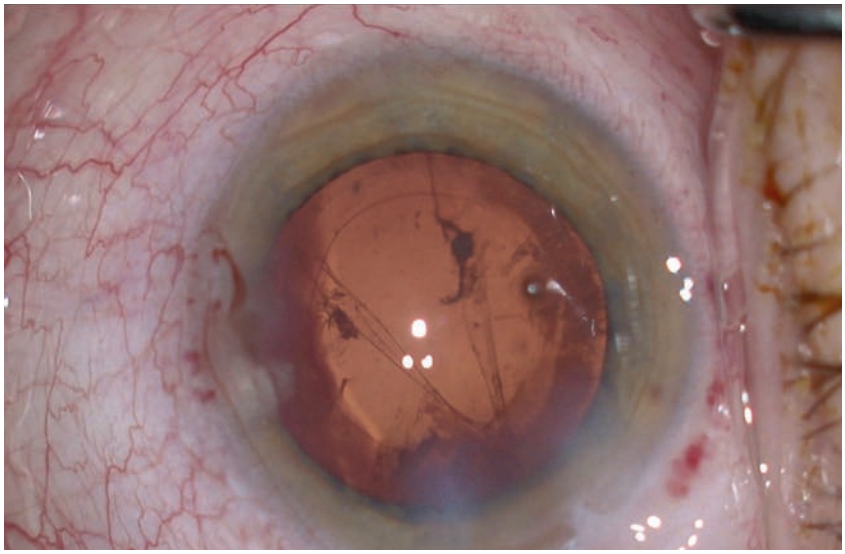
HORIZON

have to change plans in the middle of the procedure. This is going to throw off my schedule. We're going to fall behind.' You have to block out all these self-defeating thoughts, deal with the situation, and make the best decisions you can under the circumstances to achieve the best result you can for your patient."

Dr. Lee emphasizes that you shouldn't stop irrigation and pull the phaco tip out of the eye right away. "If you do this, of course, the vitreous prolapses forward and possibly out through the incision," he notes. "Traditionally and classically, dispersive viscoelastic is best to use in this situation, but the reality is that you have to use whatever is open. Your priority is to stabilize the eye and regroup.

"You have to pause and get members of the OR staff ready to help you," he continues. "Tell them what equipment you need for dealing with the complication. Usually, I'll administer a sub-Tenon's block to make the patient more comfortable. You're going to be manipulating the sclera and the case is going to take longer. At that point, your main goal is to try—if you can—to keep fragments from falling back through the posterior capsule rupture."



Douglas K. Grayson, MD

Figure 3. Intact anterior capsule with a tear in the posterior capsule after cortical removal.

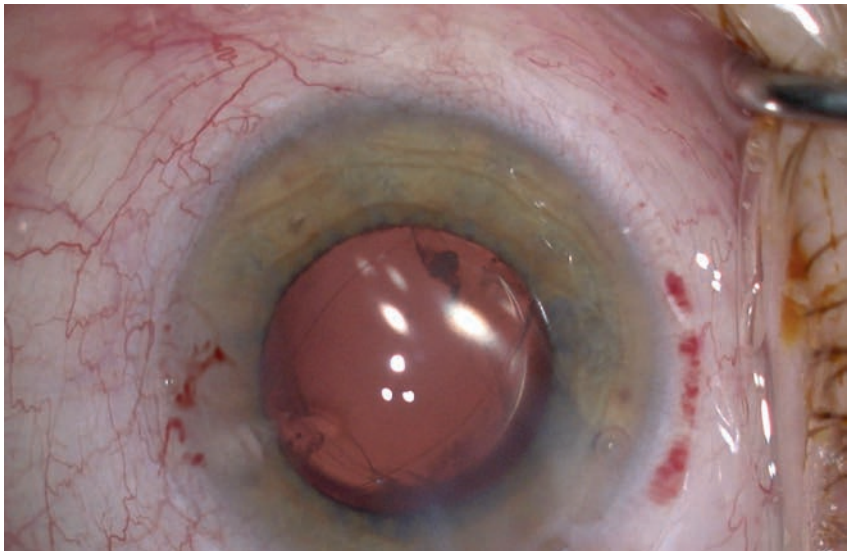


Figure 4. Stability of toric IOL position with anterior capsule capture

Effective Vitrectomy

In these cases Dr. Al-Mohtaseb recommends performing an anterior vitrectomy by going through pars plana (posteriorly) instead of through a corneal wound (anteriorly). "This way, you pull back vitreous and avoid traction," she says. "I use Kenalog to not only highlight the vitreous but to provide an anti-inflammatory effect. I also use Miochol-E (acetylcholine chloride intraocular solution) at the end of the procedure to make sure the pupil is round. Then I suture the wound."

Dr. Lee does a vitrectomy with a split infusion. "I make a sclerotomy to do my vitrectomy," he adds. "Some surgeons aren't comfortable making a sclerotomy and prefer to go through the limbus. Anatomically, the use of a sclerotomy offers the benefit of being more posterior, so that you're more likely to keep the vitreous back. If you're not comfortable making a sclerotomy, you can still do a good cleanup through the limbus. However, you definitely have to split the infusion and the vitrector. It's important to know your machine and it's settings."

Dr. Lee starts his vitrectomy in the ICA (irrigate, cut, aspirate) mode, using a high cut rate that exceeds 2,000 cuts per second. At the end of the case, like others, he almost always use acetylcholine to constrict the pupil and to help maintain eye pressure. "I'm also checking for residual vitreous," he adds.

Dr. Grayson does a vitrectomy through a sideport paracentesis. "All the machines currently have 25-ga. high-speed cutters," he notes. "I create a paracentesis for infusion and

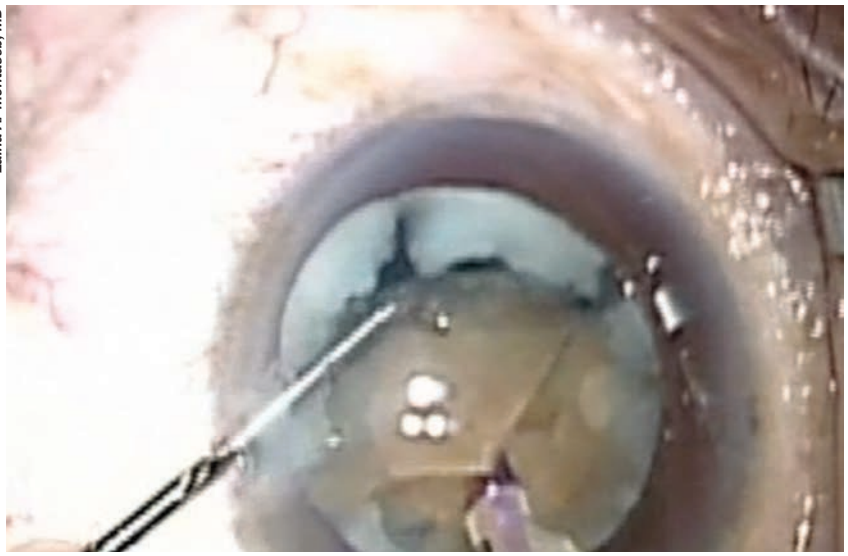

Zaina Al-Mohtaseb, MD

Figure 5. Great care is taken to chop this dense cataract; dense lenses are risk factors for a ruptured posterior capsule.

put the cutter through the other side. Then I just clean up the vitreous in the anterior chamber and clean up the anterior vitreous in back of the posterior capsule. I don't think anterior segment surgeons should start doing posterior stabs and going after nuclear pieces that have been dislocated into the posterior vitreous. If a nuclear fragment does go into the posterior segment, the best thing for us to do is to continue cleaning up the anterior vitreous and then determine whether you can put in some kind of a lens."

Besides vitrectomy—and adding miotics—Dr. Wallace recommends that you consider doing a peripheral iridectomy. "This can pull the iris material away from the angle, avoiding a potential blockage that could develop with all of the activity present in that area," he says.

Completing Surgery

When completing cataract surgery after stabilizing the eye, Dr. Al-Mohtaseb says she rarely puts a one-piece lens in the bag, unless it's a very small circular rupture. "I recommend implanting a three-piece lens in the sulcus, relying on optic capture," she says.

Like Dr. Al-Mohtaseb, most surgeons seek alternatives to a single-piece IOL for these patients. "You occasionally will see a case in which surgeons will place a single-piece acrylic IOL in the bag, such as when they're able to turn the tear in the posterior capsule into a posterior capsulorhexis," says Dr. Lee. "But I would just go to a three-piece IOL."

After a posterior capsule rupture, Dr. Lee explains that IOL stability can still be achieved even when the optic and haptics need to go into the sulcus, despite the misgivings of some surgeons. "If you can't capture the optic, you can stabilize it by suturing the haptics to the iris," says Dr. Lee. "But to be honest, it can be kind of hard to do that in this type of situation, when you have an unplanned vitrectomy. So it's fine to put the lens in the sulcus and finish up the case. You can go back later to deal with the lens or suture it to the iris for more support—saving that part for another day, basically."

Dr. Lee cautions inexperienced surgeons to not place a three-piece intraocular lens for the first time in a complicated cataract case. "It's best not to try to learn how to do this implantation under these conditions," he says. In his surgery center, however, where all of the surgeons are experienced, a three-piece is used as the default monofocal. "I'm very comfortable using a three-piece monofocal in all circumstances," he notes.

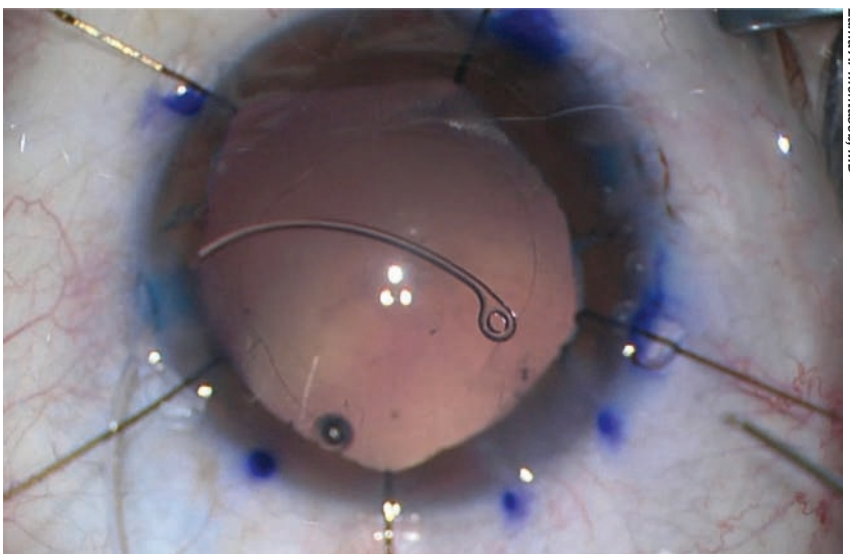

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Figure 6. In a patient with poor dilation and weak zonules from pseudoexfoliation, iris hooks and a capsular tension ring are inserted to reduce the risk of complications such as a posterior capsular rupture.

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

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

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

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

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

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

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

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

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

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REVIEW

Refractive/Cataract Rundown

Multifocal Uncertainty

After a posterior chamber rupture, Dr. Grayson says you may need to change plans if you were about to implant a multifocal IOL.

"Optimally, any IOL placed in the sulcus should have an anterior capsule capture for stability," he says. "It's advisable to use three-piece IOLs in the sulcus." He notes that the only available three-piece multifocal IOLs you can use in the sulcus are Alcon's Restor 3.0 IOL and Johnson & Johnson Vision's Tecnis ZMAOO three-piece +4.0.

If the anterior capsule is not present enough for some degree of IOL capture, however, Dr. Grayson says the use of a multifocal may not be advisable at all. "That's because a sulcus-placed IOL may move slightly," he says. "This isn't usually an issue for a monofocal IOL, but it may impact the optics of a multifocal. That changes your surgical planning for patients receiving multifocal IOLs, especially if your patient is scheduled to receive PanOptix or TECNIS Symfony IOLs."

Even when implanting monofocal IOLs, of course, IOL power adjustments may be needed, Grayson continues.

"If it's a pure sulcus placement, you should go half a power down on the IOL," says Dr. Grayson. "But if you're doing an IOL capture, I'd say you need to only decrease the power about a quarter of a diopter. You could potentially use the same lens. It's important to make a compensation with the A-Constant as well."

Taking a different approach, Dr. Lee says if you're able to place the haptics in the sulcus and capture the optic, you should be able to keep the lens very stable and eliminate the need to change the IOL power. "If you're not able to capture the optic of the IOL and need to place the optic in the sulcus, then of course you have to make IOL power adjustments," he says.

When Dr. Al-Mohtaseb achieves an optic capture, she also doesn't feel a need to adjust her IOL calculation. In the absence of an optic capture, she tries to avoid placement of the IOL in the sulcus, given the risk of the lens rubbing on iris, especially in myopic eyes. "In kids, I'd consider a posterior capsulorhexis, given the risk of posterior capsular opacification formation," she adds.

Prolonged Cases

Dr. Grayson, like Dr. Lee, doesn't think implantation of an IOL after a posterior chamber rupture is essential. "I'm thinking of an example of a long case involving a very hard cataract, after you've done a vitrectomy," he says, "if you don't get the lens in a good position, especially when you're trying to place a sulcus lens with optic

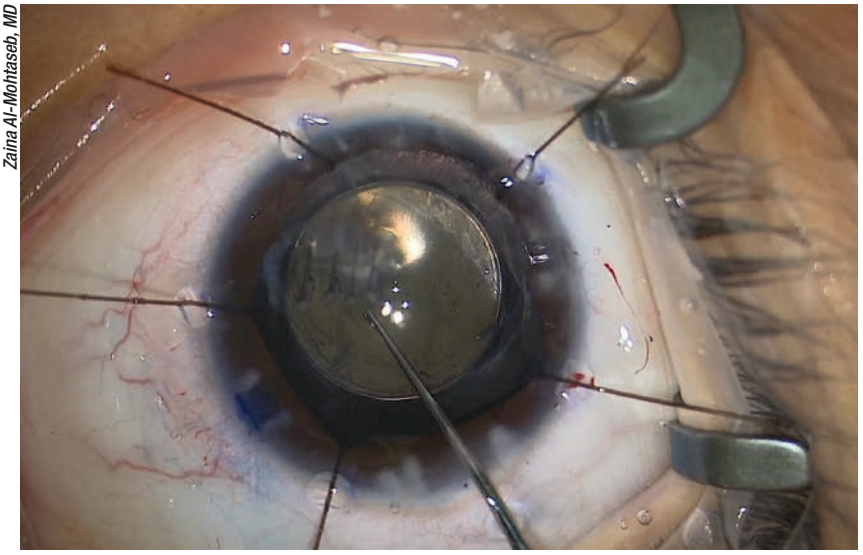
Zaina Al-Mohtaseb, MD

Figure 7. A three-piece lens is inserted into the sulcus with optic capture in a child with a corneal laceration, traumatic cataract, and posterior capsular violation from trauma.

capture, or if you're using an anterior chamber lens, you need to consider leaving the patient aphasic and coming back later. I've been in situations in which these patients start to move all over the place, and you start losing control. It's totally acceptable to leave the patient aphakic, put a suture in the wound and come back another day to put in a secondary lens, especially if that patient is coming back for a secondary procedure to remove a retained lens fragment with a retinal specialist. You can just leave it and do it at the same time as the retina procedure. Another option would then be for the retina specialist to place a lens either in the sulcus or with posterior suture fixation, perhaps using the Yamane technique."

After prolonged surgery associated with a posterior chamber rupture, Dr. Grayson advises you to wait until the patient's cornea has calmed down before operating on the eye again. "You could have a few visits before you're ready to go," he says. "You just need to tell the patient, 'We can fix it but we have to let the eye heal to get the best possible outcome.' You don't want to stuff a lens into an inflamed eye. Make sure the eye has healed and there's no cystoid macular edema. You can easily wait two months before putting in a sulcus lens."

Retinal Referral

"If you have any concern for retinal pathology or if you see any lenticular material in the vitreous, I'd recommend sending your patient to a retinal specialist," says Dr. Al-Mohtaseb. "Some surgeons even consider sending all patients with posterior chamber ruptures for an exam by a retina specialist."

Dr. Wallace agrees. "Of course, if there's any question about nuclear material in the posterior segment, you should send patients to a vitreoretinal surgeon," he says. "Referral to a retinal specialist is a good idea after any of these cases. The specialist can provide a second opinion and determine if any second surgery needs to be done. And the sooner you make that referral, the better. The longer you wait, the higher risk your patient has of developing posterior segment problems such as cystoid macular edema."

Dr. Lee, who also often refers patients for retinal follow-up, takes a different approach than some of his colleagues. He says he finds that retinal specialists prefer that he put an IOL in when the posterior capsule ruptures. "I always try to have an IOL in the eye at the end of the case," he says. "The only exception is if I have an IOL that dislocated posteriorly; then I certainly want to leave the patient aphakic. But that's rare situation. Referring a patient to a retinal specialist

(Continued on page 67)

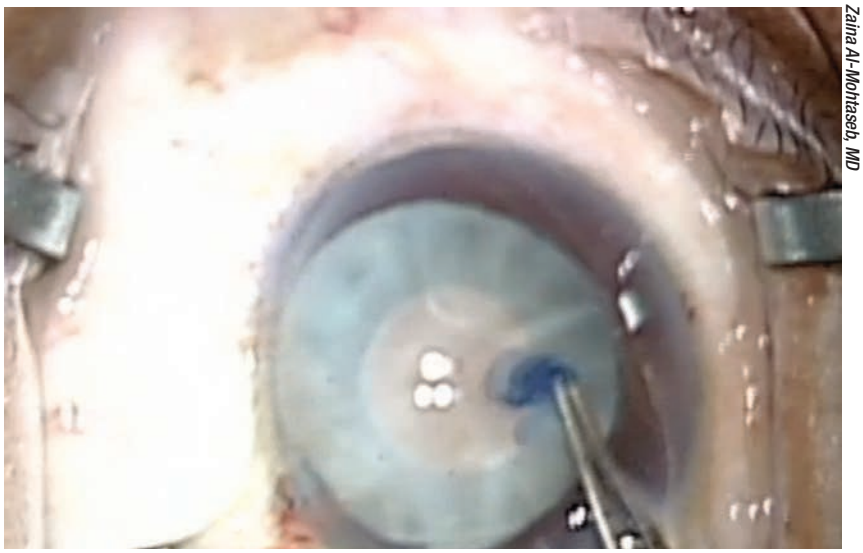
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Figure 8. Trypan blue is used in this case to help with visualization during the capsulorhexis creation in a dense cataract.

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Monoclonal Antibodies For Ocular Symptoms

Neuro-ophthalmologists review two new drugs that can treat the ocular manifestations of giant cell arteritis and Graves' disease.

Christine Leonard, Associate Editor

Tocilizumab and teprotumumab have been approved for treating giant cell arteritis and Graves' disease, respectively. Here, we'll take a look at what neuro-ophthalmologists have to say about these new treatments and how they can improve the standard of care for these diseases' ocular complications.

Tocilizumab (Actemra)

Subcutaneous tocilizumab (Genentech/Roche) is now the only drug approved for treating giant cell arteritis in adults. GCA is an inflammatory disease of the small-to-medium-sized arteries that usually manifests with headaches, weight loss, scalp tenderness or jaw claudication. It's more prevalent in women than in men, and the likelihood of developing the disease increases with age. "Someone who is 80 years old is more likely to get it than someone who's 60," says August L. Reader III, MD, FACS, a neuro-ophthalmologist in practice at Pacific Eye Associates in San Francisco. "Patients can have strokes, heart attacks, abdominal infarctions—anything that has an artery in it can become inflamed, decreasing circulation to that tissue."

This humanized monoclonal antibody was first approved in 2010 for treating rheumatoid arthritis, and approved a year later for treating systemic juvenile idiopathic arthritis. "It has a long history of treating these diseases, and that gave people confidence that it could be used in GCA as well because we already knew what the side effects were," says Dr. Reader. "The preliminary trial took place in Switzerland on five patients with GCA who were on prednisone. With tocilizumab, they were able to get them off the steroid quicker."

Tocilizumab works against the interleukin-6 receptor, a main inflammatory cytokine that modulates the body-wide immune response. But as with any drug that represses the immune system, Dr. Reader says clinicians should be mindful of current and past patient medical history. "You should not prescribe this drug if the patient has an active infection, a compromised immune system, a history of tuberculosis or hepatitis B, or if they live in an area with a high prevalence of fungal infections, such as the Ohio and Mississippi River valleys and the Southwest," he says.

Tocilizumab has no ocular side effects, but Dr. Reader says you should monitor your patient's blood work carefully. "Patients can get neutropenia or thrombocytopenia from this medication," he says. "They may also have increased liver function enzymes that will increase their lipid profile, so be sure to watch for elevated cholesterol and triglyceride levels."

Ocular Manifestations of GCA

In the eye, the biggest problem caused by GCA is an acute ischemic optic neuropathy. Patients can go blind from this disease complication, and until the introduction of tocilizumab, glucocorticoids were the only treatment.

"When you have someone with an acute ischemic optic neuropathy, elevated sedimentation rate and C-reactive protein and the classic symptoms, we put them on high-dose steroids immediately to protect the other eye," Dr. Reader says. "The original studies decades ago showed that if you put the patient on steroids immediately,

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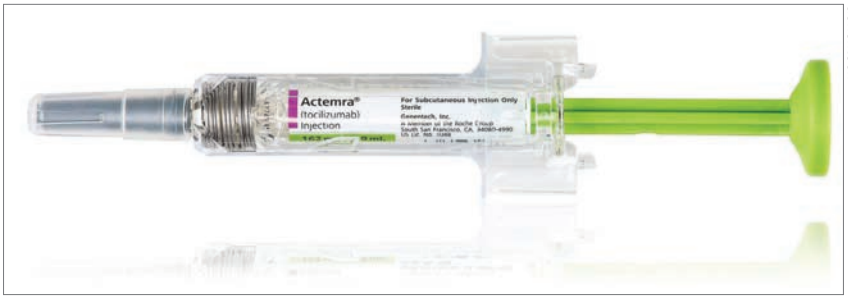
there's a good chance you can protect the other eye from getting it; however, if they get it in one eye and don't go on steroids, there's a greater-than-50-percent chance that it'll go to the other eye in three weeks. That's why getting the patient on steroids is so essential: to protect second-eye vision."

Dr. Reader says he checks for elevated sedimentation rate and C-reactive protein when patients are referred to him with headaches. If they're also presenting with the classic symptoms, he begins steroid treatment immediately. Typical steroid dosing for GCA is 60 to 80 mg per day. "We monitor patients closely based on sedimentation rate and C-reactive protein, and as they get better, we reduce the steroids based on the blood-work numbers. In most cases, before tocilizumab, patients would remain on steroids for about two years, slowly tapering. Studies show that giant cell arteritis sort of burns itself out after about two years, so if you get them on steroids, your biggest problem is mainly the steroid side effects. That's why tocilizumab is a real breakthrough for this disease."

Tocilizumab Studies

"Two studies showed that tocilizumab therapy significantly increased the number of GCA patients that remain in remission after tapering off corticosteroid therapy, compared with placebo-treated patients," says Kenneth S. Shindler, MD, PhD, a professor in the departments of ophthalmology and neurology at the University of Pennsylvania's Scheie Eye Institute in Philadelphia.

In the first study in *The Lancet* in 2016,[1] 20 patients received tocilizumab subcutaneously and 10 patients received the placebo. Both groups were given oral prednisolone. "This study showed that at the end of the full dosing period (24 weeks), there was an 85-percent response rate, and they were able to get patients off steroids in about 12 weeks," says Dr. Reader. "Only 40 percent of the placebo group achieved remission. At one year, 85 percent of the treated group was still relapse-free, whereas only 20 percent of the placebo group was relapse-free."



Genentech

Tocilizumab (Actemra) 162-mg pre-filled syringe for self-injection (also available in an autoinjector pen). Tocilizumab should not be administered during an active infection.

The researchers found that the mean survival-time difference to stopping steroids was 12 weeks in favor of tocilizumab, which they noted led to a cumulative prednisolone dose of 43 mg/kg in the tocilizumab group versus 110 mg/kg in the placebo group after one year. Half of the placebo group patients experienced serious adverse events, compared to seven patients (35 percent) in the treated group.

The major FDA trial for the efficacy and safety of subcutaneous tocilizumab included 251 patients with GCA, divided into four groups to receive subcutaneous tocilizumab (at a dose of 162 mg/kg) weekly or every other week combined with a 26-week prednisone taper, or placebo with a prednisone taper over a 26- or 52-week period.[2] Here are some of the findings:

- At week 52, 56 percent of patients treated with tocilizumab weekly and 53 percent on the every-other-week dose achieved sustained remission.
- At week 52, 14 percent of the placebo group on the 26-week prednisone taper and 18 percent on the 52-week taper achieved sustained remission. These differences between the tocilizumab and placebo groups were significant ($p<0.001$).
- Cumulative mean prednisone dose over one year was 1,862 mg in the tocilizumab groups, 3,296 mg in the placebo group on the 26-week taper and 3,818 mg for the 52-week taper ($p<0.001$).
- Anterior ischemic optic neuropathy developed in one patient in the tocilizumab every-other-week group.

Both studies support the use of tocilizumab for GCA, but Dr. Shindler notes that the continued need for a fairly long course of corticosteroids is still a limitation. "From the perspective of an ophthalmologist," he adds, "the studies weren't designed to examine effects in those patients that specifically present with ocular manifestations of GCA. Those patients may have unique disease susceptibility that may or may not respond to tocilizumab as well as patients without ocular manifestations of their GCA."

Dr. Shindler says that it would be good to know if tocilizumab is effective in suppressing GCA without the need for concurrent steroid treatment, but he adds, "I suspect this would be difficult to study, given the long history and successful use of steroids."

Dr. Reader says studying the use of tocilizumab alone as an initial treatment for GCA will also likely be difficult because the chance of vision loss from acute ischemic optic neuropathy is too great a risk.

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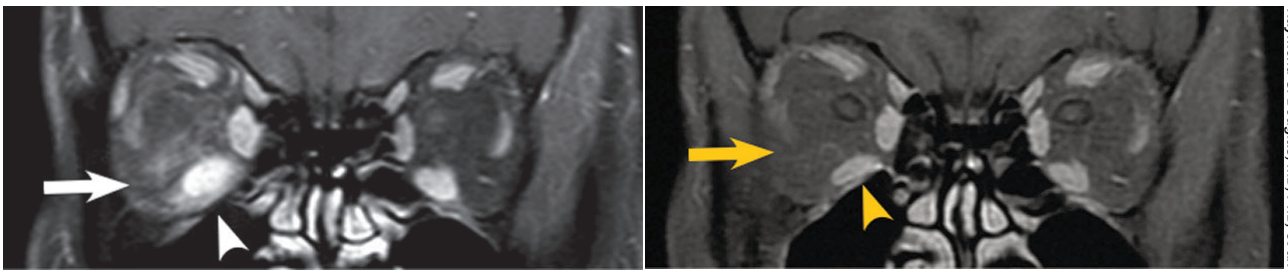

Raymond S. Douglas, MD, PhD, et al.

Coronal, contrast-enhanced, fat-saturated, T1-weighted MRI scans of a patient from the Tepezza clinical trial who was treated with teprotumumab.[4] At baseline (left), protopsis measured 23 mm and Gorman subjective diplopia score was 3 (range: 0 to 3), with enhanced orbital fat (white arrow) and enlarged inferior rectus muscle (white arrowhead). At 24 weeks (right), protopsis measured 18 mm and Gorman subjective diplopia score was 0, with no inflammatory signs or symptoms and a reduction in both orbital fat (yellow arrow) and inferior rectus muscle volume (yellow arrowhead).

rheumatologist. The recommended dosing for GCA is one prefilled syringe of tocilizumab (162 mg) once a week, in combination with a tapering steroid treatment. Dr. Reader notes that for patients under 100 kg of weight, every-other-week dosing is preferred. "There's an initial loading dose, and then it's double the dose every three weeks thereafter for a total of eight infusions, either IV or subcutaneous injection," he says.

"Just as with any medication that reduces the immune response, be wary of secondary infections," Dr. Reader continues. "Most of these patients are already on steroids before they start tocilizumab, which would reduce their resistance even further. Preventing and watching out for new infections or exacerbations of infections is key. Tocilizumab decreases the white blood cell count and platelet count in the body."

Teprotumumab (Tepezza)

Teprotumumab-trbw (Horizon) was approved on January 21 for treating active Graves' disease in adults, based on two multinational clinical trials. "This drug was developed specifically for Graves' disease and it's the first drug approved for it," Dr. Reader says. "Everything we've used in the past has been off-label, like corticosteroids, azathioprine and methotrexate—mainly cancer drugs with variable responses. That's why it's exciting to have something specifically for Graves' disease. Teprotumumab will make a huge difference in lessening the treatment burden."

Teprotumumab blocks insulin-like growth factor-1, which is elevated in those with Graves'. As a thyroid hormone disease, Graves' disease is usually treated by an endocrinologist.

"In Graves' disease patients, the muscles and fat around the eye become inflamed and cause proptosis," Dr. Reader says. "This leads to different side effects of exposure such as dry eye and double vision because of the muscle enlargements."

He says that Graves' disease-related eye problems have always been challenging to treat. Steroids have been the go-to therapy, as well as radiation and surgery. "Studies out of the Mayo Clinic demonstrated that if someone is steroid-sensitive, has Graves' disease and is beginning to experience severe side effects from steroids, orbital radiation to kill the inflammatory cells and decrease the muscle size is effective," he says.

"Usually the patients who receive radiation are the ones with double vision," he continues. "We also see a reduction in diplopia [with radiation]. A patient may come in with 20 D of hyperopia and 15 D of esotropia or exotropia and the steroids just don't clear it up. We do the radiation, specifically to the affected muscles causing the diplopia, and in most cases, we're able to get the eyes back together close enough to allow us to control the disease with a little bit of surgery, or in some cases, just prism and glasses."

Dr. Reader reminds us that, so far, no treatment has been perfectly successful, but in severe cases, invasive surgery has helped. "In extreme cases where the proptosis is so bad that it's constricting the optic nerve and the patient is starting to lose vision, we do an orbital decompression," he says. "This involves going in surgically and removing the two lateral walls and roof of the orbit—removing the muscles—so this enlarged tissue mass can expand into those areas and give relief to the optic nerve. But that's rarely done today and only in extreme cases. I think I've had only three cases in the past 10 years that required surgery."

Safety and Efficacy

The original safety study for teprotumumab, done in two arms, included 170 patients—84 received the drug and 86 received a placebo.[3,4] "In the first arm, proptosis improved by 2.5 mm in the treated group but only 0.2 mm in the placebo group," Dr. Reader says. "The response was 69 percent in the treated group and 20 percent in the placebo group at 24 weeks ($p<0.001$)." The only drug-related adverse event in the first arm was hyperglycemia in patients with diabe-

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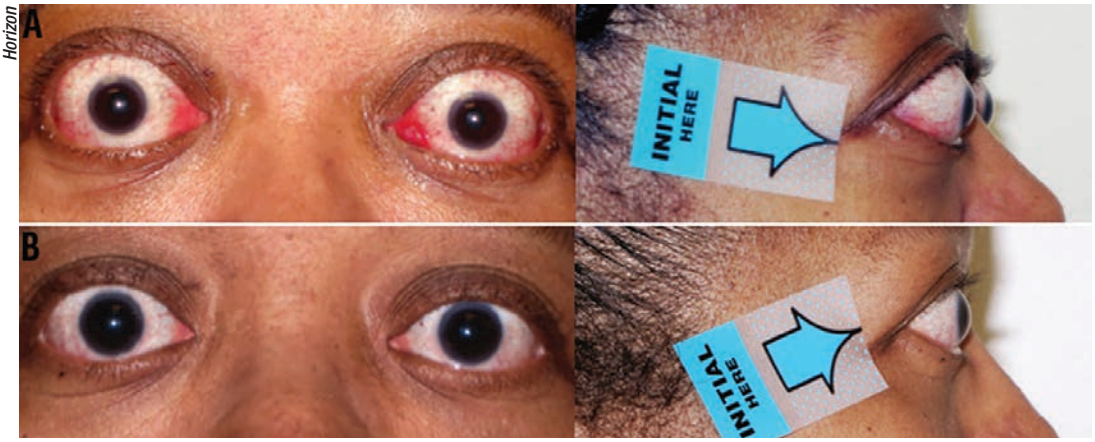

Before (A) and after (B) treatment with teprotumumab for Graves disease.

tes, which was controlled by adjusting their diabetes medication.

"In the follow-up study (41 treated, 42 placebo), the response rate was 83 percent among treated patients and 10 percent among the placebo group," he continues.[4] "The reduction in proptosis was 2.8 mm in the treated group and 0.5 mm in the placebo group. Of all the patients in the beginning of the study, 73 percent had diplopia, and at the end of the 24-week study, diplopia was gone in 54 percent of the treated group and in 25 percent of the placebo group."

"These two clinical trials demonstrated significantly better improvement in multiple features of thyroid-related orbitopathy, including proptosis and clinical activity scores in patients treated with teprotumumab compared to patients treated with placebo," Dr. Shindler says. "Additionally, the studies were well-designed and the benefits were convincing without significant or serious adverse effects. One potential limitation is that the results weren't directly compared with pulsed intravenous steroids, which are often used for active thyroid orbitopathy."

Teprotumumab is relatively safe, as far as side effects are concerned, but the drug may cause hyperglycemia and exacerbate existing irritable bowel disease. "If someone is diabetic or glucose intolerant, teprotumumab may worsen or kick them over into diabetes," Dr. Reader explains. "That's occurred in about 10 percent of patients in studies. Then with IBD, where patients already have reduced IGF-1, adding anything that will further reduce IGF-1 will make the disease worse."

Per the final FDA approval, teprotumumab is administered intravenously. "Patients start off with an initial dose of 10 mg/kg and then three weeks later they're given 20 mg/kg," Dr. Reader explains. "They do the 20 mg/kg for six more sessions, for a total of one 10-mg/kg and seven 20-mg/kg infusions. The infusion goes in over about an hour and a half, but those who tolerate it well may take it over one hour."

Lessening Treatment Burden

Both tocilizumab and teprotumumab stand to lessen the treatment burden for their respective diseases, which, as Dr. Shindler notes, are currently treated—with varying success—with corticosteroids, which themselves carry the potential for significant adverse effects.

"The data for each therapy is compelling," he says. "They suggest that these drugs should become important options for standard-of-care therapy in appropriate patient populations—e.g., GCA patients that can't wean off of corticosteroids without signs of relapsing and thyroid orbitopathy patients with active, progressive disease.

"The studies suggest roles for both therapies as first-line agents," he continues, "although I suspect they likely will be used more as second-line agents for a while, given a number of factors, including cost of therapy and current practice patterns using corticosteroids that may be difficult to convince practitioners to replace. For teprotumumab, one barrier is the complex nature of the thyroid orbitopathy disease that has made it difficult to quantify features that define the disease state in each patient."

Another barrier is cost. Dr. Reader says that, without insurance, cost may be a major obstacle for accessing these drugs; it runs in the thousands of dollars, unlike corticosteroids. "Monoclonal antibodies are expensive to develop," he says, "and since these diseases affect only a small percentage of the population, their use will be niche and it may take several years before the cost begins to come down." REVIEW

Dr. Reader and Dr. Shindler have no related financial disclosures.

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Paul M. Larson, MBA, MMSc, COMT, COE, CPC, CPMA

2021 Eye Exam Coding Changes

A look at the Evaluation and Management coding changes that are causing a stir in ophthalmology.

Q I understand that my eye exam codes are changing in January 2021. Is that true?

A Yes. It's a really important change—but just to the Evaluation and Management outpatient (office-based) exam codes. Those are codes 99202 to 99205 and 99212 to 99215.

Among the important changes for this 992xx exam code series is that using the history and the exam for the purposes of choosing a code are minimized, although they will remain important to documenting the reason for visits and for liability protection. Additionally, if you use inpatient hospital exam codes, those are staying the same for 2021, although they are slated for significant changes in 2022 or later.

Q What is happening to the Medicare payments for eye exams in 2021?

A For medical visits, the proposed rule shows large changes in what doctors will be paid next year. It's not final, but all of the Eye codes (92002 to 92014) are going down in value; in many cases the drop is significant. New patient E/M codes 99202 to 99205 also go down—but established patient E/M codes 99212 through 99215 are all proposed to rise significantly in payment. We should see the Final Rule and payment announcement around the first of December.

Here are the current payment amounts for 2020 and the proposed changes for 2021 (National Medicare rates):

National Medicare Rates

CPT	2020	2021	CPT	2020	2021
99205	$ 211.12	$ 210.66	99215	$ 147.76	$ 172.27
99204	$ 167.09	$ 159.37	92014	$ 128.12	$ 119.04
92004	$ 152.66	$ 141.30	99214	$ 110.43	$ 122.91
99203	$ 109.35	$ 106.14	92012	$ 89.86	$ 84.20
99202	$ 77.23	$ 69.04	99213	$ 76.15	$ 86.78
92002	$ 85.53	$ 80.97	99212	$ 45.77	$ 54.20

Q That sort of decrease sounds awful. What alternatives are there?

A Some important things to remember are that the average eye practice sees about 80 percent established patients, and only 20 percent are new patients. Although the Eye codes are all going down, an E/M code is also possible, and often will pay more in 2021 when the

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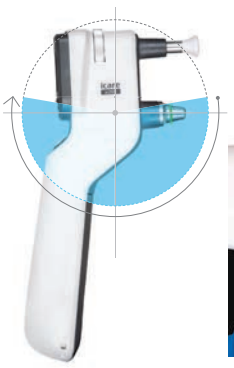

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patient is established. Moving to E/M codes from Eye codes in a meaningful way can largely mitigate the potential revenue hit.

Q What about the Eye exam codes? If I still get better payment on the Eye code, are the rules for using them changing?

A The familiar Eye exam codes we commonly use: 92002; 92004; 92012; and 92014, don't change in documentation or coding requirements and there's no move to change them. If the eye code pays better than the E/M code that you can also code for, then stay with it.

Q I heard the level 1 exam codes are being deleted. Is that true?

A In 2021, E/M exam code 99201 is being deleted, but it's of little consequence since eye doctors almost never use this code anyway.

On the established-code side, 99211 remains and is unaffected because it's not a doctor-exam code. Payment has been and remains low even though it's forecast to go down about $0.80 from 2020. You can still use it in the limited circumstances where it still fits.

Q How likely is it that implementation would be delayed?

A First, it is highly likely that this implementation will happen. A delay is very improbable. Both AMA (CPT) and Medicare support the change. Second, if it goes through, the changes will be followed by all of your other payers. Be prepared!

Q Are the new E/M rules truly de-emphasizing the history and exam?

A Yes. The new 2021 guidance notes that these two important components in the current 2020 rules are going to be "as medically appropriate"; the doctors decide what's needed to support the patient and their condition at that visit. Of course, there are also important liability concerns in terms of each of these areas and you shouldn't lose sight of that—they can't be ignored.

It's highly likely that this implementation will happen. The AMA and Medicare support it.

Q I heard that there are two ways to choose an E/M code in 2021. Is that true?

A Yes. The most common way will be to use medical decision making. The other way is to use physician time. Each has been redefined in significant ways.

Q How is coding E/M via time different?

A In general, the time a provider spends on the exam, both face-to-face and non-face-to-face, counts if it's not being separately reimbursed. For example, say the doctor sees a glaucoma patient and spends 25 minutes total, but five of that is looking at the billable OCT and VF done that day. Since the OCT and VF are being billed, only 20 minutes can count. Also, there are different time standards for new vs. established patients. Coding by time for a new patient begins at 15 minutes and at 10 minutes for established. Any less than those values and selection of the level of service is impossible for E/M. Eye codes don't have a time option.

Q If I'm not using time, and exam and history are less relevant to coding level, how is the decision-making method used?

A There are three areas, and each uses a different methodology and guidance than the current ones use.[1] It's impossible to delve deeply into the many changes in a short article, but under the current rules, coding for a new patient is different than an established patient. In 2021 this will always be following the "2 out of 3" rule. No longer will new patients be coded as "3 out of 3."

The three areas are 1) Problems, 2) Data, and 3) Management. For the Problems area, the number and severity of the problems, whether they are different than the last visit and their timing/frequency all play a part. Data is more complicated in the new guidance and is unlikely to be relevant to coding for eye-care providers, as we will most often use Problems and Management to arrive at a code level. Management involves how the patient is treated and the urgency of the treatments. Medical decision-making will be the more common method of choosing a code level, except for certain situations (one example is providers who do low-vision examinations). REVIEW

Mr. Larson is a senior consultant at the Corcoran Consulting Group and is based in Atlanta. He welcomes comments or questions on the topic of this month's column. Please contact him at plarson@corcoranccg.com.

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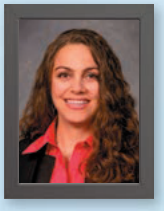
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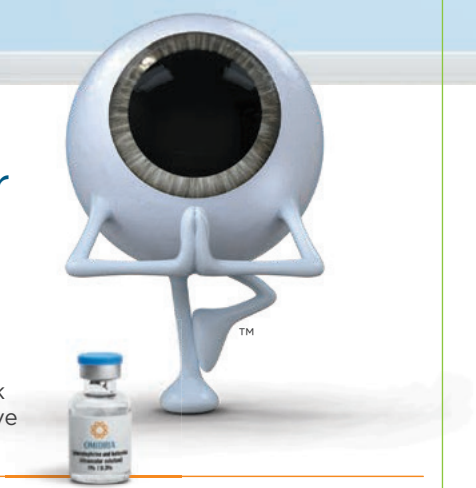

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INDICATIONS AND USAGE

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References: 1. Omeros survey data on file. **2.** OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017. **3.** Al-Hashimi S, Donaldson K, Davidson R, et al; for ASCRS Refractive Cataract Surgery Subcommittee. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg*. 2018;44:1032-1041.

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Ophthalmologists in the Machine: The AI Era

Christine Leonard, Associate Editor

Experts discuss the upsides and downsides of AI and the new FDA-approved devices for diabetic eye disease.

Artificial intelligence is well-suited to ophthalmology, where data- and image-heavy subspecialties easily supply the large quantities of data required for training neural networks. Now, for the first time in any medical field, fully-autonomous AIs have come to primary care settings to diagnose diabetic eye diseases. Experts say these AI systems will help to identify many more patients in danger of losing vision, and with more sensitivity than a retinal specialist. But despite these recent breakthroughs, AI developers say you won't be out of a job just yet.

In this article, we'll cover some of the nuances of AI and take a look at the two autonomous ophthalmic AI systems currently available.

Send in the Bots

Experts predict that AI will play a major role in the early detection of diseases like diabetic retinopathy and diabetic macular edema. In 2019 alone, approximately 463 million adults were living with diabetes around the world, and this number is expected to grow to an estimated 700 million by 2045.[1] Almost 80 percent of those with diabetes live in less-advantaged countries, where access to medical care—and to ophthalmologists in particular—may be limited. With an epidemic of these proportions, scaling up screening measures with AI technology can alleviate some of the burden.

Placed in a primary care setting or endocrinologist's office, AI for diabetes can improve patient outcomes and lower direct patient costs.[2] During their annual checkups, those with diabetes are recommended to undergo a diabetic eye exam by a general ophthalmologist or retinal specialist. However, Michael D. Abràmoff, MD, PhD, the developer of the IDx-DR and a professor of retina research at the University of Iowa Hospitals & Clinics, points out that the most recent studies show that only 15 percent of people with Medicare insurance get this annual diabetic eye exam. "We also know that this noncompliance results in preventable vision loss or blindness. AI can help by performing the eye exam during the same primary-care visit," he says.

This type of triage by AI is not only more convenient for the patient, but would also have major ripple effects throughout the health-care system. As an example, Dr. Abràmoff recalls his time in New Orleans, introducing an AI system in the wake of Hurricane Katrina. "After Katrina, there was no eye care left in New Orleans," he says. "People with diabetes went to their

This article has no commercial sponsorship.

diabetes clinics and were told to go to their eye exams, but the wait time was more than four months and nobody went. Instead, they began losing vision and going blind. Nine months after introducing an AI for diabetic eye exams, the wait time for seeing an eye-care provider was the same day. We're seeing similar effects from AI with the current COVID-19 situation. Patients are fearful of going to an additional appointment for their diabetic eye exam, but the exam can be done during their regular visit with AI."

The Centers for Medicare and Medicaid announced in August that Medicare will pay for autonomous AI. The new CPT category 1 code for autonomous AI is 9225X.

IDx-DR

The IDx-DR (Digital Diagnostics, formerly IDx) is an autonomous AI designed to detect diabetic retinopathy and diabetic macular edema, and the first FDA-approved autonomous AI in any field of medicine.

Since its approval in 2018, this device has been in use across the country, from Stanford and Johns Hopkins to the Mayo Clinic and even in supermarkets in Delaware—and the list of locations keeps growing. The American Diabetes Association has also issued updates to its recommended standard-of-care practices to include autonomous AI for diabetic eye exams.

The IDx-DR autonomous AI system from Digital Diagnostics.

IDx-DR is indicated for adults over the age of 22 who haven't been previously diagnosed with diabetic retinopathy. The AI system is compatible with the nonmydriatic Topcon TRC-NW400 digital fundus camera, but IDx-DR's developer Dr. Abràmoff says this device isn't for ophthalmologists or optometrists. "It's primarily for primary care and designed to be used by an operator who's only minimally trained," he says. "IDx-DR fits easily into the workflow of primary care. Patients undergo their diabetic eye exams, and then by the time they've had blood drawn and their blood pressure and weight measured, the eye exam results are back, and the primary-care doctor can then go over them with the patient, as well as review all other aspects of diabetes."

In the 2017 pivotal trial, IDx-DR was validated against clinical outcomes, including OCT, and demonstrated 87-percent sensitivity and 90-percent specificity for detecting more-than-mild diabetic retinopathy.[3] "Most importantly, it met our 'diagnosability' endpoint," Dr. Abràmoff says. "Diagnosability is your validated diagnostic result for a certain number of patients. A study might exclude a portion of participants if the system performed poorly on them and report good performance in a small subset of patients. But AI systems must work on the vast majority of people with diabetes in this country. If the AI performs well on only a small subset of patients, it's not good enough. In IDx-DR's case, diagnosability was 96 percent in a large, diverse population. The result is either positive or negative, so only 4 percent of the time did the AI say, 'I don't know.' That's very important."


The EyeArt AI system (Eyenuk) requires no software downloads or installations, and generates individual diagnostic reports for each eye.

Dr. Abràmoff says the IDx-DR is invariant for sex, age and race because it's designed around biomarkers in an attempt to mimic the thinking process of a human clinician. "We have different detectors for hemorrhages and for microaneurysms," he says. "The AI analyzes the patient images and the detectors either fire or don't fire. Then the outputs are combined."

EyeArt

The autonomous AI system EyeArt (Eyenuk) received approval in August of this year for detecting more-than-mild and vision-threatening DR in adults. It's the first FDA-cleared autonomous AI technology that produces diagnostic outputs for each of the patient's eyes.

"EyeArt is approved for screening patients who are diabetic and who don't have any known retinopathy," says Jennifer I. Lim, MD, the Marion H. Schenk Chair in ophthalmology and director of the retina service at the University of Illinois at Chicago,

YOUR PATIENTS WITH DME ARE READY FOR A CHANGE

The power of EYLEA improved and sustained outcomes in the largest phase 3 anti-VEGF clinical trials completed to date in DME (N=862), with improved visual acuity at 52 and 100 weeks.[1]

IMPORTANT SAFETY INFORMATION AND INDICATIONS

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen with 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

EYLEA IMPROVED AND SUSTAINED VISION GAINS THROUGH 52 AND 100 WEEKS IN DME[1-3]

	EYLEA 2 MG EVERY 4 WEEKS[§]	EYLEA 2 MG EVERY 8 WEEKS[‖]	CONTROL
VISTA	(n=154)	(n=151)	(n=154)
MEAN CHANGE IN BCVA (52 WEEKS,* 100 WEEKS[†])	+12.5, +11.5 LETTERS	+10.7, +11.1 LETTERS	+0.2, +0.9 LETTERS
PROPORTION GAINED ≥15 LETTERS (52 WEEKS,[‡] 100 WEEKS[†])	41.6%, 38.3%	31.1%, 33.1%	7.8%, 13.0%
VIVID	(n=136)	(n=135)	(n=132)
MEAN CHANGE IN BCVA (52 WEEKS,* 100 WEEKS[†])	+10.5, +11.4 LETTERS	+10.7, +9.4 LETTERS	+1.2, +0.7 LETTERS
PROPORTION GAINED ≥15 LETTERS (52 WEEKS,[‡] 100 WEEKS[†])	32.4%, 38.2%	33.3%, 31.1%	9.1%, 12.1%

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received 1) EYLEA 2 mg administered every 8 weeks following 5 initial monthly doses; 2) EYLEA 2 mg administered every 4 weeks; or 3) macular laser photocoagulation (control) at baseline and then as needed. Protocol-specified visits occurred every 28 (±7) days. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52, as measured by ETDRS letter score.

Efficacy of both EYLEA groups was statistically superior vs control at 52 and 100 weeks ($P<0.01$).

*Primary endpoint.

[†] Prespecified exploratory endpoint.

[‡] Secondary endpoint.

[§] Last observation carried forward; full analysis set.

[‖] Following 5 initial monthly doses.

The results of exploratory endpoints require cautious interpretation and could represent chance findings, as a multiplicity adjustment has not been applied.

anti-VEGF = anti–vascular endothelial growth factor; BCVA = best-corrected visual acuity; DME = Diabetic Macular Edema; ETDRS = Early Treatment Diabetic Retinopathy Study.

See more at HCP.EYLEA.US

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology*. 2014;121(11):2247-2254. doi:10.1016/j.ophtha.2014.05.006 **3.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology*. 2015;122(10):2044-2052. doi:10.1016/j.ophtha. 2015.06.017

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

08/2020
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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:

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 CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following 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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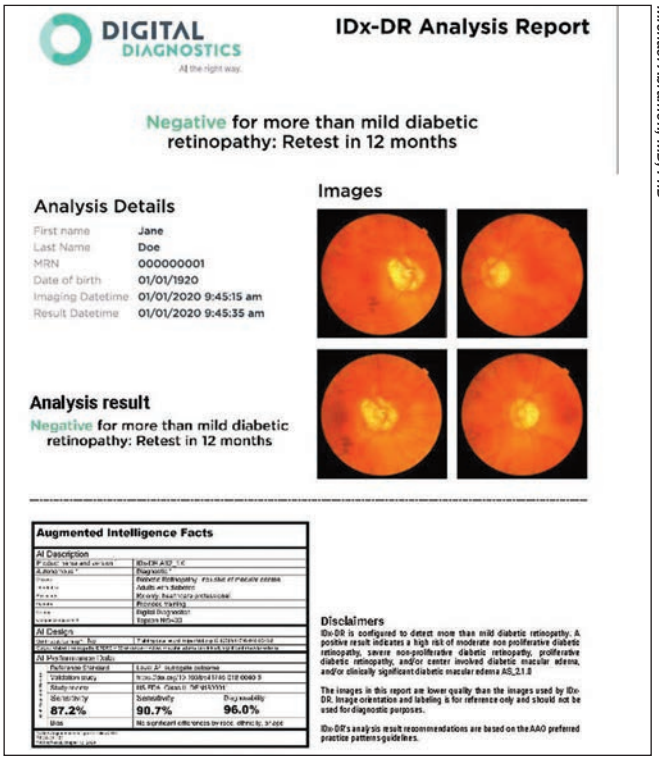
Illinois Eye & Ear Infirmary. "The patient has two nonmydriatic, 45-degree photographs taken of each eye. If the image isn't good enough, the AI will indicate that you need to dilate, but for the most part dilation isn't necessary. Before the patient leaves the office, the readout is generated, which tells the patient whether to come back in a year or to see a retinal specialist or eye-care provider for high-risk PDR or severe NPDR, for example." EyeArt can also determine whether there is clinically significant macular edema in addition to diabetic retinopathy, says Dr. Lim.



An example of a diagnostic report from the IDx-DR. Unlike assistive AIs, autonomous AIs are capable of making medical decisions with no human oversight. Unlike telemedicine exams, in which images must be sent off for human grading, autonomous AIs provide point-of-care diagnoses and triage so that patients can receive their diagnosis and directions for next steps before they leave their primary care appointment.

EyeArt is currently compatible with two nonmydriatic retinal cameras, the Canon CR-2 AF and the Canon CR-2 Plus AF; it functions on a cloud-based system. "There's no software to download or install," Dr. Lim points out. "You just take the fundus photo and it's sent up to the cloud, where the AI cloud-based software analyzes it. The result is sent back within a minute to the local computer. It's much faster than a typical telemedicine reading of the image."

In the clinical trial, EyeArt demonstrated 96-percent sensitivity and 88-percent specificity for detecting more-than-mild DR; for detecting vision-threatening DR, EyeArt showed 92-percent sensitivity and 94-percent specificity.

Another study (which was funded by the National Institutes of Health and undertaken both by employees of Eyenuk and independent researchers from the Doheny Eye Institute) tested EyeArt's diagnostic efficacy retrospectively in a real-world setting, analyzing 850,908 fundus images of 101,710 consecutive patient visits from 404 primary care clinics.[4] The researchers found that 75.7 percent of visits were nonreferable, 19.3 percent were referable to an eye-care specialist and in 5 percent the DR level was unknown, per the clinical reference standard.

In this case series, EyeArt demonstrated 91.3-percent sensitivity and 91.1-percent specificity. For the 5,446 patients with potentially treatable DR (more-than-moderate NPDR and/or diabetic macular edema) 5,363 received a positive "referral" output from the EyeArt system, showing a sensitivity of 98.5 percent. The researchers concluded that their study supports the value of AI screening in the real world as an easy-to-use, automated tool for endocrinologists, diabetologists and general practitioners for DR screening and monitoring.

Michael Abràmoff, MD, PhD

The Physician vs. The Machine

Critics of AI screening systems are quick to point out the "tunnel vision" inherent in these devices. When patients visit the clinic, they're screened by an ophthalmologist for a number of ocular diseases—cataracts, glaucoma, diabetes, tumors—but the two AI systems currently in use look for only the diseases they're trained for. Some worry about what's being left out.

Dr. Lim acknowledges the limited screening scope but believes that the alternative—not being screened at all—carries more serious consequences. And, she notes, these AI systems will occasionally identify nondiabetes-related conditions, albeit in a roundabout way.

AIs are not immune to type 1 and 2 errors and will sometimes misdiagnose patients, but even if the result is a false positive, Dr. Lim says the AI is likely picking up on pathology that needs further examination anyway. "If the AI sees something abnormal in the fundus images, it may read it as a false positive and that may trigger a normal DR diagnosis," Dr. Lim explains. "In our pictures for the EyeArt system, there were a few cases of false positives, and for the most part the actual diagnoses were macular degeneration or choroidal nevus, or some other disease for which that person should be seen by an eye-care professional.

"The downside would be if you have a false negative," she continues. "The rate of false negatives is very low,

though, and in the event the system misses disease, it's often still mild NPDR stages. The AI system did not miss high-risk PDR or very severe NPDR cases."

In spite of the occasional false positives or negatives, Dr. Abràmoff says the machine's accuracy can be impressive. "In fact, AI's accuracy is higher than mine as a retina specialist," Dr. Abràmoff says. "If you look at studies for sensitivity, it's actually higher than in other studies that compare board-certified ophthalmologists to the same standard. Their sensitivity is about 30 to 40 percent, and for the AIs, its closer to 90 percent."

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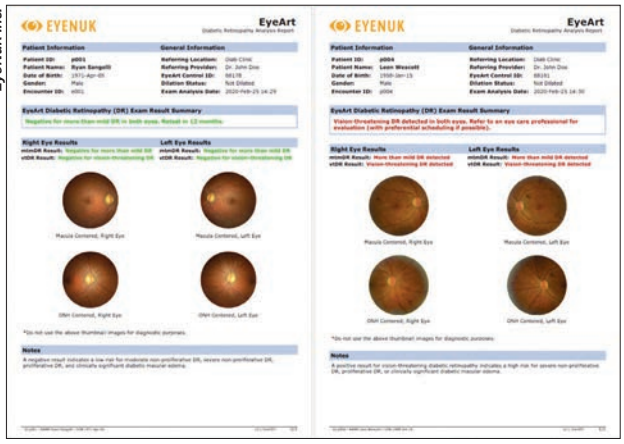

Two examples of EyeArt analysis reports. On the left, the patient is negative for more-than-mild diabetic retinopathy, and on the right, the patient receives a positive diagnosis for vision-threatening diabetic retinopathy. Positive analysis reports indicate when a referral is needed. Experts note that the images on the reports are valuable tools for patient education.

This may sound a little frightening, but Dr. Lim reassures us that retinal specialists aren't missing vital pathologies. "When retinal specialists look at an eye, they aren't going to miss PDR for the most part," she explains. "But they might under-grade, and in fact, that's what we found when we did the EyeArt studies that compared physician DR grading of an eye to both the reading center and AI grading methods.

"Retinal specialists' sensitivity for dilated ophthalmoscopy overall is 28 percent, compared to 96 percent with the EyeArt system," Dr. Lim continues. "But retinal specialists' specificity is higher—99.6 percent, versus 87 to 88 percent with the EyeArt system. That's because if there's some other disease present, we'll diagnose what it is; we aren't going to mistakenly diagnose it as DR."

Dr. Lim says that when compared to general ophthalmologists, the retinal specialists were found to exhibit higher sensitivity—59.5 percent versus 20.7 percent—and comparable specificity at around 99 percent for detecting mild NPDR. The reason for this low sensitivity compared to the AI, Dr. Lim explains, is once again a tendency to under-grade.

"We might grade the DR as mild, but the machine and the reading center may grade them as moderate," she says. "There's a certain number of hemorrhages needed to cross a diagnosis threshold, and perhaps the specialists missed a few of these hemorrhages. In mild NPDR, you can only have a microaneurysm—you can't have hemorrhages. For the most part these images were mild, and as I noted before, retinal specialists didn't miss any cases of sight-threatening retinopathy. Some were missed by general ophthalmologists, but this number was very low, and only around 19 percent of their false negatives were more severe diabetic retinopathy. The bottom line is that AI performs quite well compared to reading centers and certainly—unfortunately for us—performs better than retinal specialists looking at an eyeball."

As with any new technology, we often wonder about obsolescence. Will reliance on AI fundus image interpretation negatively impact the next generation of retinal specialists' ability to read the same images? Will we even teach it to future students? Dr. Lim says that probably won't be an issue. "We're still going to be seeing patients with the pathology," she says. "We aren't an image-only type of discipline, and there will always be patients who come in because they can't see or because they've been referred by the AI machine. So we'll still need to take a look at the eye and know how to interpret what we see and make a diagnosis. The only difference will be that we won't be seeing as many normal or very mild cases, because the AI will have screened out those less severe cases."

In this way, Dr. Lim says that AI can help improve workflow. "With an AI system screening and redirecting those with DR, we can become more focused on the patients needing treatment, since only those with significant DR will be sent to us," she says.

Tech-side Manner

Unlike the AIs envisioned by Hollywood or even IBM's relatively amiable Jeopardy! champ Watson, these ophthalmic screening systems can't offer the personal contact or counseling of a real ophthalmologist. "When I see a patient, I emphasize control of blood pressure, blood sugar, cholesterol, hemoglobin and A1c, and a machine is just not going to do that for you," Dr. Lim says. She suggests that patient literature accompanying a diagnosis could have this information added to it. "I also really urge the AI system developers to include lifestyle advice, or to at least have the person taking the pictures emphasize it. If the screening is being done in a primary care setting, then hopefully the patient is getting the message from their primary care doctor."

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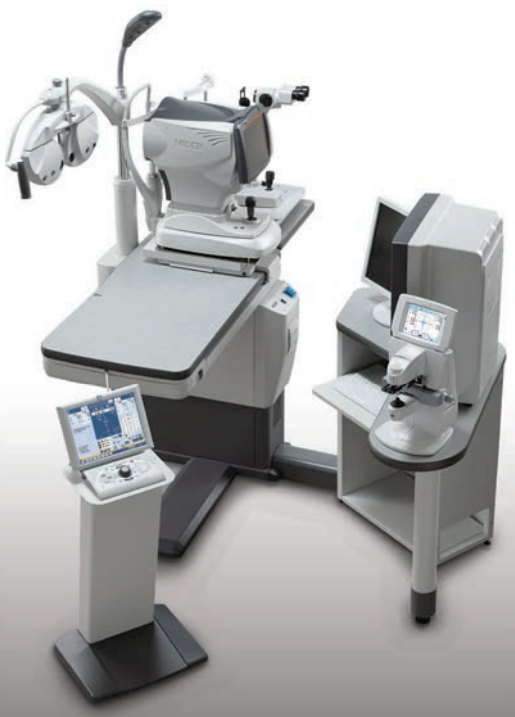

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Best Practices

Autonomous AI systems have enormous potential for good in the medical field. However, Dr. Abràmoff points out that, at its core, AIs must be ethical in order to provide these benefits. In a paper published earlier this year in the *American Journal of Ophthalmology*, Dr. Abràmoff and his co-authors conducted a literature review of bioethical principles for AI and proposed a set of evaluation criteria. He notes that these evaluation rules can help physicians understand the benefits and limitations of autonomous AI for their patients.[5]

Here are the five key ethical principles he says AIs should fulfill:

- ***Improve patient outcomes***.
- ***Be designed in alignment with human clinical cognition***. "You need to understand how the AI works and arrives at a diagnosis," Dr. Abràmoff says.
- ***Be accountable for the data***. "Ensure patients understand what happens to the data, that the data isn't sold or used for something else," he says. "That's a big fear among patients."
- ***Be rigorously validated for safety, efficacy and equity***. "People are worried about racial and ethnic bias, so in both the design and the validation, you need to minimize bias and essentially eliminate it," he says.
- ***Have appropriate liabilities***. Dr. Abràmoff and his team first proposed that liability ought to lie with the AI creator. "That's now part of the American Medical Association's policy, to make sure AI creators and companies are liable for the performance of their AIs," he says.

"These are important principles and best practices for how to deal with AI," Dr. Abràmoff says. "Validation in peer-reviewed literature, pre-registered trials and comparisons against the outcome are all key. Many AI studies you see compare AI to physicians. But the physicians themselves have never been validated against clinical outcomes. What patients care about is the effect—the clinical outcome. Does the patient see better or worse? We should be evaluating AIs based on how they perform against the outcome."

Michael Abràmoff, MD, PhD

Studies indicate that the diabetic eye exam is the most cost-effective intervention for diabetes-related complications.[7] In a case study in New Orleans, in the aftermath of Hurricane Katrina when wait-times to see ophthalmologists for diabetes-related eye exams were up to four months, the IDx-DR helped to reduce the backlog of more than 805 previously undiagnosed patients who completed their annual DR exams. A quarter of patients were found to have potentially blinding disease.

Mitigating Bias in AI

Creating an ethical AI starts with the development process and the type of data on which you train it. "You need to design AI from the ground up to minimize bias," says Dr. Abràmoff. "If you don't, you can have all sorts of very weird associations.

"AIs trained only on large data sets are essentially association machines that learn to associate an image with a diagnosis, but without understanding at all what they do," Dr. Abràmoff continues. "The AI knows about pixels in the image, numbers for each point in the image, and it associates the numbers with the diagnosis, but it doesn't understand what a hemorrhage is and it doesn't understand what an optic disc is, or a blood vessel, or a fovea. It only knows these pixel values and the diagnosis. And so if you ask, 'Why did you decide this patient had diabetic retinopathy?' it can't tell you the patient had three hemorrhages and some exudates. It can tell you that some pixels were more important in terms of making a decision than others, which is what many people talk about when they do post hoc justification for these AIs."

Dr. Abràmoff says for this reason having insufficient examples of all races or ethnicities in your training data set is the biggest problem. "The background color of the retina can vary greatly among different ethnicities," he says. "An AI may be really good at associating images with the diagnoses you gave, but if you have a patient whose fundus image doesn't resemble what's in the training data, the AI won't perform well."

Having lots of examples in your training data isn't enough to ensure a lack of bias, though—it's impossible to account for every retinal variation. That's why understanding how the AI reaches its decision is also key. When a clinician looks for biomarkers such as lesions or exudates, the color of the retina doesn't matter, Dr. Abràmoff says. "If they have these lesions, then they have diabetic retinopathy. You either have lesions or you don't."

Both the IDx-DR and EyeArt algorithms detect lesions from diabetic retinopathy. AIs that can detect specific biomarkers and retinal pathology are more likely to be invariant for race, age and sex. A recent OCT-based algorithm in Korea trained on 12,247 OCT scans of South Korean patients seemed to appropriately focus on the differences within the macular area to extract features associated with wet AMD. The research team validated their findings in an ethnically diverse population in the United States of 91,509 OCT scans, and accuracy remained high. They noted, however, that their next hurdle is understanding how the algorithm classified and

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Data Gaps and Algorithmic Stewardship

Algorithms are only as good as the data on which they learn, and a historical bias toward collecting data on white males has led to significant sex and race data gaps that continue to adversely affect their respective populations.[1-3,5] However, blindly adjusting algorithms for race can also adversely affect minority populations if algorithms confound the influence of race with variables such as socioeconomic status and access to primary health care.[4]

An increasing number of publications have reported instances of racial bias in AI algorithms and other data-driven diagnostic tools.[5-6] One such report that found that circumpapillary capillary density measured by OCTA in patients with open-angle glaucoma demonstrated greater accuracy for those of European descent than those of African descent. Another study found that in a commonly used commercial algorithm that identifies patients with complex health needs, black patients assigned the same level of risk were consistently sicker than white patients. This bias arose because the algorithm determined risk based on predicted health-care costs, rather than illness; unequal access to care has led to less spending on care for black patients. The authors reported that fixing this disparity would increase the percentage of black patients receiving help from 17.7 to 46.5 percent.

To counteract the structural racism built into these algorithms, health professionals recommend routine reviews and audits of currently used AI algorithms and machine-learning technologies.[7] Atul Butte, MD, PhD, of the Bakar Computational Health Sciences Institute at the University of California, San Francisco, points out that algorithm stewardship has become necessary to ensure the safety, efficacy and fairness of algorithms. In his recently published article in *JAMA*,[7] he says that health systems should designate a person or group to perform these audits, advised by clinicians familiar with the language of data, bioethicists, patients, scientists and safety and regulatory organizations.

—CL

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diagnosed disease.[6]

Another way AI developers insure against bias is careful training and regular evaluation of reading center graders. "The EyeArt system software was trained on hundreds of thousands of images from multiple large databases that were read by reading centers," Dr. Lim says. "These reading center graders score the level of DR on a scale of one to 100 for DR, with levels of 35 or higher indicating more-than-mild DR. Images may be graded as anything in between—level 35, 45, 57 or 58, for example—and graders are compared both to each other and to their own previous work to provide checks and balances on their grading and ensure uniformity and adherence to standards. As a result of these grading standards, graders have become more adept and consistent in their evaluations of fundus images." (*For further reading on how bias influences AI algorithms, see the sidebar above.*)

Standardizing AI

Dr. Lim is part of the Collaborative Communities on Ophthalmic Imaging, which was created by the FDA and Stanford University. "We're bringing people together into teams for different diseases such as AMD, glaucoma, diabetes and ocular tumors to figure out AI standards and what we need to set up AI so that people can use it." Dr. Lim is part of the AMD CCOI group.

Dr. Abràmoff heads up the Foundational Principles of Ophthalmic Imaging and Algorithmic Interpretation group, which includes entities such as the FDA, the Federal Trade Commission, Google, Microsoft, IBM, Apple and a host of bioethicists and workflow experts. "Our goal is to have a bioethical foundation for how we build, validate, test and deploy AI within hospital systems and without," he says. "Many of the AIs out there now assist the doctor in making a decision, and the doctor is ultimately liable for that decision, but autonomous AIs make the decision themselves." REVIEW

Dr. Lim has no related financial disclosures. Dr. Abràmoff is the founder and executive chairman of Digital Diagnostics. He has patents and patent applications related to IDx-DR and is an investor in the company.

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How to Plan Your Exit Strategy

Sean McKinney, Senior Editor

Unique strategies are needed to engineer such a life-changing transition during the COVID-19 pandemic. Here's what to consider.

Bellwether shifts in procedural volume, practice patterns and profitability brought on by COVID-19 have prompted many ophthalmologists in private practice to rethink when and how they will walk away from their life's work. Old assumptions have faded in the minds of aging practitioners as they explore future opportunities. Other physicians are exploring mergers with bigger practices and selling to private equity firms.

The need has never been greater for updated insights on valuating your practice, understanding the current practice-sale market, marketing your practice to ideal buyers and stepping down as an employee or independent contractor before making a graceful and worthwhile exit from the practice you've sold.

In this report, experts offer insights on their experiences, and advice on how you can respond wisely to today's unexpected and, to some extent, unprecedented challenges.

Exploring Your Options

Although COVID-19 is stirring thoughts of career change, exit strategy choices remain the same, according to John Pinto, founder of J. Pinto & Associates, an ophthalmic practice consulting firm in San Diego. He summarizes each option:

1 ***Winding down and closing.*** "We see this approach when there are no likely buyers for your practice," Mr. Pinto observes. "Or when you've exhausted all opportunities to divest your practice. This happens a lot in the rural Midwest and areas where it's difficult to recruit doctors. A significant number of small, rural practices are closing each year, as boomer-age doctors fail to find buyers. If you can't find a buyer, you may have to simply wind down operations and sell your tangibles for salvage value." To avoid abandoning your patients, he adds, you can provide them with their charts (if they want them) or send the charts to practices where your patients ask the charts to be sent, which Mr. Pinto says is routinely done. You may also store the charts or convey them to a colleague who's willing to act as a custodian or who may be able to care for your patients, depending on their interests and needs. "Laws vary state by state on how to do this," says Mr. Pinto. "It would be best to contact your state medical society and discuss your options with your attorney."

2 ***Traditional approach.*** "In this familiar model, you hire a

new partner-tracked associate a few years before retiring," he says. "In a larger practice, you'll see a revolving carousel of doctors at different ages—a few beginning their careers, a few close to retiring and most in their mid-careers. We see this approach in the most-stable practices, which are now on a third generation of doctors. However, fewer practices are falling into this category."

3 ***Sell to a "near-lying" practice.*** A near-lying practice might belong to a friendly colleague or nominal competitor. "Most practices are worth more to near-lying practices than they are to doctors just getting out of training," Mr. Pinto says. "Certainly, if you're ready to sell, it's reasonable to look around your neighborhood to see who might like to take over."

4 ***Sell to a health-care system.*** These opportunities are rare because ophthalmology, typically detached from acute-care centers, is not an admitting specialty. "But some local health-care systems are building eye-care departments, so one might just be interested in your practice," he adds. "Generally, though, the payment you'd receive for this sale would be about half of what you'd receive from a doctor-to-doctor sale of your practice."

5 ***Sell your practice to a private equity firm and stay on board.*** "Payment for your practice is as much as twice what you'd receive from a doctor-to-doctor transaction," says Mr. Pinto. "It can be like manna from heaven if you're nearing retirement, allowing you to extract as much value from your practice as possible. The downside is you'll have less control over administrative and clinical areas. For our mid-career clients, we find that the benefits are somewhat more equivocal."

6 ***Merge your practice with a larger, compatible practice.*** In this scenario, you may transition from owning 100 percent of your practice to a fractional share of the larger practice. "It may make sense for docs under certain circumstances—if you're in your 50s and don't know if you have five or 10 years left before retiring, for example," says Mr. Pinto. "You might be getting fatigued by the administrative burden, or you might be having problems getting contracts that provide access to patients." He notes that this option can be professionally satisfying, providing access to colleagues "down the hall" when you need a second opinion, for example. It also relieves administrative burdens.

7 ***Retire from your practice but retain ownership and run it like a business.*** "This is rarely done, but I think we'll see more of this going on," says Mr. Pinto. "Under this scenario, your practice would continue as a business after you retire—or even after you expire. Your wife or other family members can take over when you're gone and run it almost like a passive investment." He says the model can be difficult to manage because you need to find cooperative doctors willing to work for a controlling outside doctor—and eventually for your family. "Not many doctors will go along with this, but it can work for an owner in a larger market, where it's harder for younger doctors to get jobs," says Mr. Pinto.

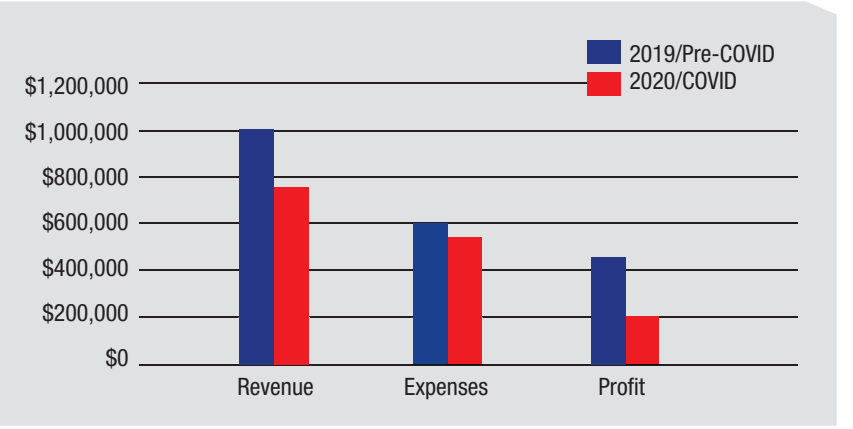
Even though each of these succession options remains viable, Mr. Pinto and other experts say you'll need to fine-tune and possibly overhaul your current practice exit plans to best position yourself in the future.

"The anxiety among ophthalmologists now is on steroids, if that makes sense," says Craig N. Piso, PhD, of Piso & Associates, a psychologist and organizational development consultant with a focus on practice management in ophthalmology. "The pandemic, economy, unemployment and other factors are pulling doctors away from their usual laser focus on what they do well. They're trying to determine what their futures might look like. I'm doing a lot of consultations."

What's Going On?

According to the American Academy of Ophthalmology, 50 percent of the 18,550-plus respondents to

COVID-19's Effect on Profits



Profit margins in ophthalmology practices typically range from 30 to 45 percent. But because practices operate primarily on fixed costs, one could experience as much as a 50-percent decrease in profits from a 25-percent drop in revenue, according to consultant John Pinto.

the most recent AAO membership survey[1] are 55 years old or older—the demographic group that's at least in the early stages of planning how and when to leave practice. A total of 57 percent are in solo or group practices, where the highest concentration of ownership stake is found.

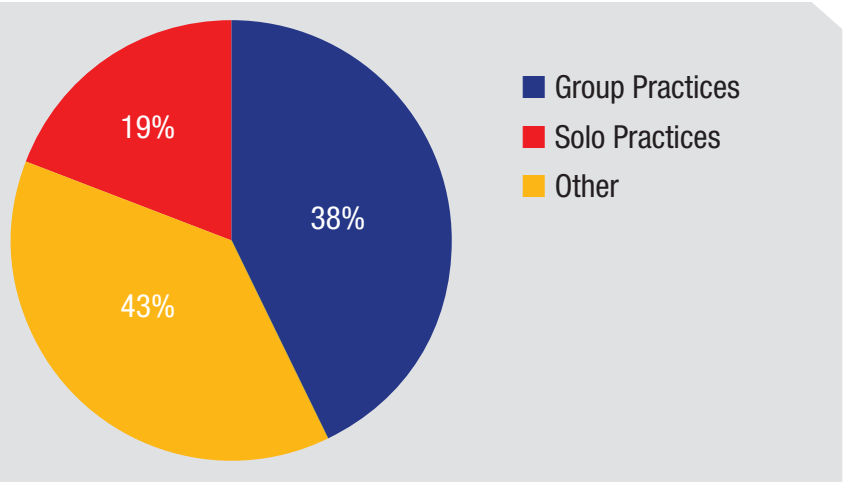
"Exit strategies are typically well thought out and flow to a certain rhythm," says Bruce Maller, founder and CEO of BSM Consulting, Incline Village, Nevada. "But the pandemic has changed the thinking of a lot of practitioners, causing them to consider different succession paths. Practices were severely disrupted when they were shut down by COVID-19 for two to three months. Of course, many have recovered, many are even operating at pre-shutdown levels. But even the recovery has been spotty, depending on where you practice and on a lot of local and regional dynamics."

"The pandemic has changed the thinking of a lot of practitioners, causing them to consider different succession paths."
— Bruce Maller

Mr. Maller sees "an overarching reassessment by practitioners" everywhere. "They're asking themselves, 'How do I want to plan my future? How does the pandemic affect us? Does it affect us to the extent that we should re-evaluate future succession options?' " he says.

Mr. Pinto notes that practices that had low profit margins before the pandemic have been hardest hit and are now burdened by uncertainty.

U.S. Ophthalmologists' Practice Settings



Nearly 60 percent of today's practicing ophthalmologists are in solo or group practices, where the highest concentration of ownership stake is found. Other settings include multispecialty (including some non-ophthalmology specialties), academic institutions, hospital/health-care systems and government/military settings.[1]

"All they had to do was modestly decrease revenue and it caused a leveraged impact on the bottom line," he observes. "Profit margins in ophthalmology practices typically range from 30 to 45 percent. But because practices operate primarily on fixed costs, one could experience as much as a 50-percent decrease in profits from a 25-percent drop in revenue. *(See COVID-19's Effect on On Profits on page 51.)* As Warren Buffet said, 'You don't find out who's swimming naked until they drain the pool.' In 2019, lots of practices appeared to be fairly vibrant. All it took was a little draining of the revenue pool, and those doctors were left naked, if you will."

Like Mr. Maller, Mr. Pinto has found in his consulting work that some practices have rebounded well despite continuing patient flow reductions needed to keep waiting rooms safe and to meet other time-consuming safety requirements during visits. "Nothing has surprised us about some practices that have sailed smoothly through this pandemic year," says Mr. Pinto. "These practices are a little smaller, so they can move faster. They have great MD/lay leadership and have a strong command of data. They could see what their capital access requirements were and where they needed to trim expenses. Also, some offices in rural areas have practiced social distancing as part of their culture for generations. These areas' populations are less affected by COVID-19, so patients are less fearful about getting back to the doctor."

How to Valuate Your Practice

Mark E. Kropiewnicki, Esq., LLM, an attorney with Health Care Law Associates and a consultant with the Health Care Group, both in Plymouth Meeting, Pennsylvania, says efforts to strengthen or at least maintain your bottom line are critical as you prepare to exit private practice by selling your practice.

"Profitability is a critical component of your practice valuation, which you want to be as high as possible," says Mr. Kropiewnicki, who works on practice sales and

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purchases, as well as practice valuations, new-doctor employment agreements, buy-ins, pay-outs and income-division arrangements.

If you're preparing to sell your practice, now is the ideal time to arrange for a valuation, being mindful that it will need to hold up to scrutiny and be flexible when negotiations over a sale ensue. A number of different types of valuation may be used, including the market-value (comparable sales) method, discounted cash flow method, multiple of earnings method and capitalization of earnings method. The type of valuation method most used by Mr. Kropiewnicki, as described below, includes an assessment of hard assets and goodwill values—only because accounts receivable are not sold in most practice sales.

Considerations include:

• ***Hard assets, including equipment, leasehold improvements, supplies and software.*** After eliminating items of marginal value, personal items and assets no longer in use, Mr. Kropiewnicki advises you to depreciate the value of countable depreciable items based on an average lifespan of 10 years—while maintaining a floor of 20 percent of original cost. For example, a $10,000 piece of equipment that you've owned for five years would be worth 50 percent of $10,000, or $5,000. If you've owned the equipment for 15 years, the value would be the floor value of $2,000. For supplies, such as drugs or optical frames, you would claim 1/12 or 1/6 of their yearly cost, depending on whether you keep one or two months worth of inventory. Or you'd do an inventory count and multiply that count by the current costs of the items.

• ***Goodwill is a benchmark value, based on comparable sales.*** "This approach would be similar to pricing a house," except you're considering the sales of comparable practices, according to Mr. Kropiewnicki. The goodwill encompasses the overall value of the ongoing concern, including charts, phone number, website, practice name, staff, seller's endorsement of buyer and seller's restrictive covenant. He notes that sellers and their brokers, attorneys, accountants or consultants may base their practices' goodwill value on a percent of gross revenue. One such percent is provided by the Goodwill Registry, the self-described largest database of health-care practice transactions in the country, published by the Health Care Group. The Goodwill Registry's average goodwill percent is based on the goodwill values of the reported transactions divided by the yearly collections of ophthalmology practices across the country.

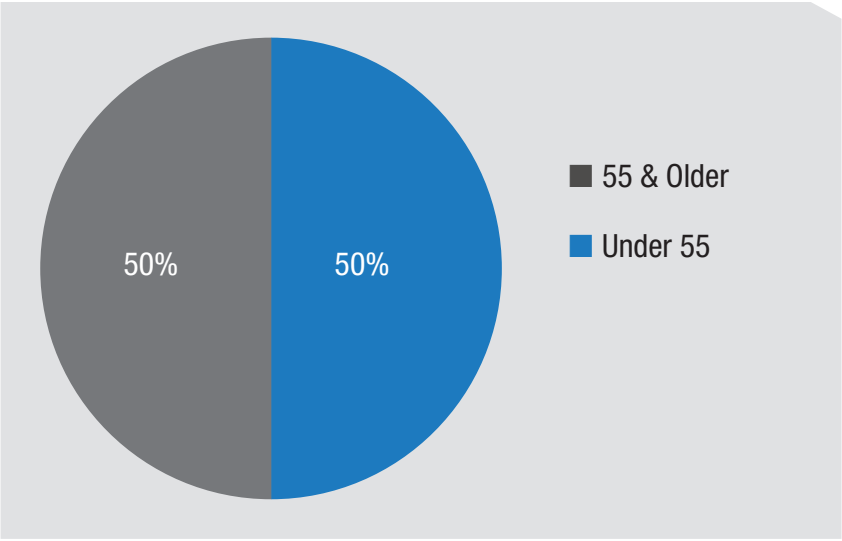
The Registry's current goodwill percent for ophthalmology practices includes a 10-year average of 30.82 percent, applied to the gross income of a practice to determine the goodwill value of an average practice.

For example, a practice that grosses $1 million should have a goodwill value of about $308,200. Added to $100,000 in hard assets and supplies, the owner of a practice might expect to sell the practice for $408,200. "But this goodwill value would be an average," Mr. Kropiewnicki emphasizes. "Your practice's goodwill total derived from this formula should be adjusted up or down according to good and bad features." Good features could include high profits, ideal location, modern facilities, moderate competition and a good mix of payers. Bad features could include low earnings, an undesirable location, heavy competition and lack of access to desired patients because of closed health-insurance panels.

Finding the Right Fit

Marketing your practice for sale successfully depends more on your

The Graying of Ophthalmology



Half of today's practicing ophthalmologists are 55 and older—the demographic group that's at least in the early stages of planning how and when to leave practice.[1]

ability to target buyers, than on the outreach you may have used to develop referral networks and attract patients in the past. "The buyer will be a specific ophthalmologist or group that, under specific circumstances, has a need to seek out what your practice offers. You could be limited to young doctors in your area or organizations with a strategic interest in moving into your area, perhaps even using the office as a satellite location," says Mr. Kropiewnicki, who will present a lecture titled *Exit Options for the Senior Solo or Sole Practice Owner* at the virtual AAO 2020 meeting this month. "You may also identify a friendly competitor from a neighboring town who wants to take over. Besides communicating your needs to trusted colleagues in the greater ophthalmology community, you could seek interested parties through the AAO or American Society of Cataract and Refractive Surgery, or you could advertise through these and other societies or professional publications."

Says Mr. Pinto: "The overwhelming majority of small private practices are either sold to young doctors joining the practice or to local competing colleagues. Larger practices are attracting considerable private equity interest. Very, very few practices are sold via a practice broker. Most transactions emerge from direct seller contact with prospective buyers."

When considering a potential sale, expert advice will be needed to structure agreements based on practice valuation, stock or asset values, payment terms, transition of ownership, implications for your practice's staff, property rental or ownership, accounts receivable, tax considerations and other factors.

Another major consideration in all sales is the potential after-sale employment of the seller as a part-timer or at a reduced capacity, according to Mr. Pinto. "Practice buyers often prefer the seller to stay on for months to years to help transition the practice," he says. "The arrangements are negotiated at the same time that the practice sale is organized. A typical scenario in general ophthalmology is for the owner to be paid plus or minus the amount of net collections."

Setting aside important details on an assortment of issues, Mr. Kropiewnicki outlines common arrangements that you can use to attract an interested ophthalmologist or group of ophthalmologists: (Note: These arrangements don't involve sales to private equity companies, which he notes aren't typically interested in purchasing small practices.)

• ***Sale to an associate.*** This transaction, involving a one- to 12-month transition, involves cash and notes paid for the practice under a stock or asset sale. One typical arrangement is that you, as the seller, would work for a negotiated period after the sale as an employee or independent contractor before retiring, usually in one year (typically preferred by the buyer) or three to five years (typically preferred by the seller). If you're selling to an associate who is already part of your practice, a sale can earn a high value. But you may need to finance most or all of the purchase price and feel comfortable with the transition terms.

Bringing on an associate for an eventual buy-in can be your most lucrative doctor-to-doctor sale option. "But that arrangement takes a long time," notes Mr. Kropiewnicki. "Six to 10 years could pass: Your associate has to finish an initial employment of 24 to 30 months, and then would begin a buy-in process that could take four to five years." He also notes the relationship could be strained by differences of opinion on fees and matters big and small or, worse, the departure of the associate before the sale is completed. "This is still the most commonly used model, however," he notes.

• ***Sale to a competitor.*** This transaction, again typically taking one to 12 months, can also result in a high value for your practice. The competitor usually doesn't need you

William Bond, MD, FASC, of Bond Eye Associates in Peoria and Pekin, Illinois, is enhancing the value of his practice with smarter use of space, including fewer seats in the waiting room (to enable distancing) and more exam lanes to maximize efficiency.

to finance any of the purchase price and often accommodates your desire to continue practicing after the sale, perhaps at a reduced capacity—such as providing only medical care—for a period of years.

• ***Merging with another practice.*** Mr. Kropiewnicki says solo practice owners aren't likely to attract many offers to merge with another practice. If such a possibility should materialize, however, the transition would typically involve a one- to six-month period. You shouldn't expect to benefit from a stock or asset sale, he adds; instead, you'd continue as an owner with a partnership interest in the practice. Under such an arrangement, you can negotiate a buy-out when you're ready to retire. The buy-out amount will depend on what the owners of the merged practice have mutually agreed to pay. There's the potential for a high-value yield for you at that time.

• ***Doing nothing.*** "This can be the comfortable decision," says Mr. Kropiewnicki. "You know what your life will look like. You could ease your workload and stress by dropping surgery when you're ready to do so."

Concerns with doing nothing are that you're still exposed to reimbursement cuts, overhead increases, regulatory requirements and other practice challenges, however.

When you're ready to sell, the value of your practice will be lower, based on reduced earnings. "It's important to remember that cutting back or dropping surgery will hurt the value of your practice," says Mr. Kropiewnicki, who notes that your health could also decline, further compromising the viability of your practice. "If you have an interested buyer for your practice, I would regard it as a bird in the hand and try to work out a deal," he advises.

A Good Time to Sell?

Mr. Maller points to one dramatic example of COVID-19-related volatility in the practice succession space.

"I was representing more than 15 practices in potential sales to private-equity-backed ophthalmic platforms," he says. "Then one day, in middle of March, it all came to a screeching halt. We were thinking the buyers wouldn't return to the market until late this year or into 2021," says Mr. Maller. "By late May through July, however, virtually every buyer was back in play. My universe of potential sales has now grown from 15 to more than 200. Owners of private practices feel that being part of something larger is going to provide security for their futures. They're willing to give up control to join a group that will help them weather another storm."

Other ophthalmologists, wary of corporate control, want to join larger private practices, according to Mr. Maller. Whether seeking more security from private equity or a larger private practice, he says the doctors express the same concerns. "They realize that being on their own, although attractive in some ways, is now too risky and challenging. The experience of COVID-19 has changed their outlook."

Experts recommend taking a hard business approach in these times, whether you plan to leave your practice through a sale, merger or retirement this year or in 10 years. "More than ever, practices should be looking at important financial keys that you can find in detailed reviews of all of your practice operations," says Mr. Maller.

Mr. Pinto couldn't agree more. "You're the top administrator," he points out. "You need to have a memorized command of important norms. Can you look through a CPT report and identify where you're under- or over-utilizing services? Can you look at your YAG rates and know whether they're within the norms and, if they're below, understand why? What's the normal percentage of cataract cases that involve a premium

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Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.

Use of corticosteroids may result in posterior subcapsular cataract formation.

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

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection.

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

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

In clinical trials, the most common adverse drug reactions were eye pain (1%) and posterior capsular opacification (1%). These reactions may have been the consequence of the surgical procedure.

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

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

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

Delayed Healing—Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and 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.

Bacterial Infections—Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

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

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

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Adverse reactions associated with ophthalmic steroids 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 Trial Experience—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse drug reactions in the clinical trials with INVELTYS were eye pain and posterior capsular opacification, both reported in 1% of patients. These reactions may have been the consequence of the surgical procedure.

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US-INV-2000053 August 2020

What Small Practices Should Know

Do you own a small practice and want to join a bigger one to protect yourself against future uncertainty? You're not alone.

"We've had practices coming to us almost on a weekly basis telling us they're not doing well and would like to align with us," says Dr. Brandon Ayres, MD, a partner at Ophthalmic Partners, a multispecialty practice with five offices in Philadelphia and nearby communities. "I frequently go to our practice administrator only to find out, after her review, that the practice won't be a good fit for us, as much as we might want to help our fellow clinicians. If we're going to onboard somebody, we have to make sure the arrangement will be at least revenue-neutral. If you have a sinking ship, and you latch yourself to mine, that doesn't help either of us. One- and two-physician practices are finding it very hard to survive. Without a highly competent administrative staff, how do you navigate through the changes in practice that we all need to keep up with?"

Some 19 percent of today's 18,550+ ophthalmologists are solo, according to the AAO.[1] Besides ensuring that they have skilled administrators, solo ophthalmologists are encouraged to take more of a hands-on role in managing their practices to better control their destinies in today's world of consolidation and competing giant practices. Here's how the Ophthalmic Partners administrator, Nancy Baker, evaluates a small practice hoping to join her six-office practice.

"Viewing a practice at a high level, I first look for synergies between our practice and theirs, and the finances," she says. "This includes practice philosophies, provider practice patterns, management styles and staff structures, as well as the accounts receivable—including total A/R days—payer groups, profit & loss, balance sheet, outstanding loans, hard assets and so on."

She also looks at staffing and the management team, including those who would be absorbed into the larger practice or who would be laid off. "I also look at the benefits offered by the other practice, compared to ours, and how the benefits would be merged. Are there any medical malpractice claims, employment practices liability insurance claims or cyber security claims? Any litigation or risk management issues?" Finally, she considers facilities issues, such a "who rents space, who owns space, whether the locations would need to merge or remain separate. Who has easy parking? What EHR/practice management systems are the practices using? These are some of the core issues to consider."

Elizabeth Keeney

Nancy Baker, administrator for Ophthalmic Partners in Philadelphia, has recently evaluated the books of several one- and two-doctor practices seeking a protective alliance with her much larger practice. None of the proposed relationships has shown the potential for even a revenue-neutral merger.

— *SM*

1. American Academy of Ophthalmology membership data. Accessed October 15, 2020. Data voluntarily provided by AAO members.

intraocular lens? Are you growing established patients by at least 5 percent per year?"

Your Tipping Point

Beyond practice valuation and developing a good exit plan, Dr. Piso, the psychologist and practice management expert who finds himself counseling more anxious doctors on how to navigate final career stages in the era of COVID-19, advises them to remember to look up from the balance sheet and CPT report so they can check up on themselves. He points out that diligence, planning and confidence are needed now more than ever to enable you to adopt the right mindset that will be critical for future success.

"Too often, ophthalmologists don't pull the trigger to make these big life changes until they hit what we call their tipping point," he says. "A tipping-point experience forces you to make changes and, as a result, makes you uncomfortable. It's critical to keep in mind that people usually have to become uncomfortable before they'll make positive changes. Rather than experiencing a negative tipping point experience that represents how you have been disempowered or makes you feel things are now out of your control, I urge doctors to be proactive. Create a tipping point of your own volition. This is what you want: To have a vision for going forward. Go for it." REVIEW

1. American Academy of Ophthalmology membership data, accessed October 15, 2020. Data voluntarily provided by AAO members.

Treatment Options for Dysfunctional Irises

Michelle Stephenson, Contributing Editor

While suture repair is an option, many patients require implantation of an artificial iris.

When a patient presents with an iris problem, deciding on the proper course of management can be challenging, since a lot depends on the cause and extent of the damage. Some cases can be well-served with a reparative surgery, while others may need an implant. Here, experts well-versed in dealing with these cases explain how they approach them.

The Patient's Plight

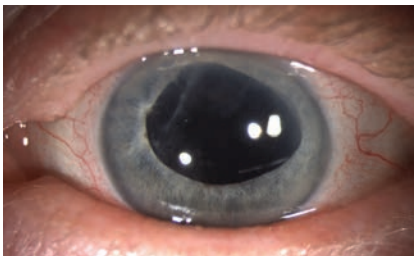
Patients with aniridia or damaged irises can suffer from severe light sensitivity and are often unhappy with the appearance of their eyes. Also, a damaged iris admitting too much light can result in reduced vision, halo and glare. Treatment options include sutures and artificial iris implantation.

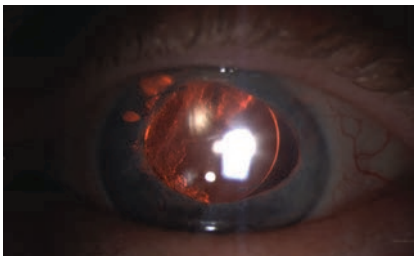
"When there is no iris or if the iris is damaged, going outside on a bright, very sunny day can be quite an issue," says Michael Snyder, MD, who is in practice at the Cincinnati Eye Institute. "While it's an issue for people with a natural crystalline lens, it can become an even bigger issue for people who have an IOL. The natural lens typically fills the entire space at the front of the eye, whereas most IOLs are about 6 mm across and only fill up about half of that diameter. So, these patients not only have excess light entering the eye, but that light is only focused when it's going through the implant. All of the light that goes around the implant causes tremendous light sensitivity and can also reduce contrast sensitivity."

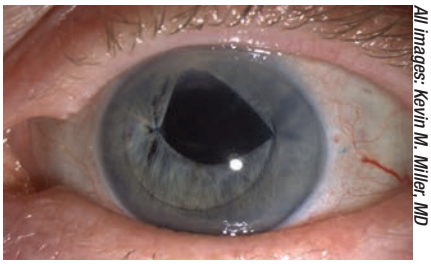
Dr. Snyder likens that reduced contrast sensitivity to someone opening the door of a movie theater during a matinee. "The projector is still focused on the screen, and the same number of lumens of light are still hitting the screen," he says. "But, now there's defocused light entering the environment, and it reduces the viewing experience. Now, imagine that you have that experience all day long when the focused light going through the lens is diminished by the defocused light going around it. Furthermore, the light that strikes the edge of the lens can cause problems with glare, arcs and halos, as well. Some folks can even have second 'shadow' images in the eye. So, it can be a really complex, vexing issue."

Some people are born aniridic, while others lose iris tissue through trauma or surgical complications. "These can result from either surgical misadventure or removal of iris or ciliary body tumors," Dr. Snyder explains.

Additionally, diseases, such as iridocorneal endothelial syndrome, can result in a damaged iris. "And, although







All images: Kevin M. Miller, MD

Figure 1A and B. The left eye of a patient who suffered corneal failure and iris trauma following cataract surgery. The posterior capsule was torn and temporal zonules were ruptured.

Figure 1C. This is the same eye after Descemet's stripping endothelial keratoplasty, suture pupilloplasty, suture fixation of the IOL and surgical posterior capsulectomy. The edge of the IOL is no longer exposed to incoming light.

their irises aren't damaged, albino patients can experience severe light sensitivity because they have no pigment in their pigment layer," Dr. Snyder adds. "While the iris is not structurally damaged, it is functionally damaged."

Treatment Options

Dr. Snyder adds that treatment depends on the extent of the damage that's present. "If a patient has a small defect from the removal of a small tumor, for example, or a small defect from a trauma, it's often possible to close that defect with sutures and apposing the edges of the iris that are there," he says. "Some people's irises are very stretchy, and you can close a pretty large defect. Other people's irises are not so elastic, and when you put a stitch in, the suture material just cheesewires through and falls out. It's difficult to predict which irises will be elastic and which irises will not. I've been surprised before. Some irises can be stretched much more than you initially think, and others really don't stretch much at all."

Kevin M. Miller, MD, agrees. "We are fairly limited in the sizes of the defects that we can close with sutures," he says. "In a patient who has a traumatic mydriasis, the pupil sphincter muscle has been ripped open. Those can often be closed with a purse-string type of pupilloplasty. In patients who have a laceration through the iris or just a small piece of the iris missing, we can often close those with sutures. We can close up to maybe a two-clock-hour sectoral defect, and we can close an iridodialysis, where the iris has been ripped away from its root," says Dr. Miller, who is in practice at the Stein Eye Institute at UCLA.

Unfortunately, the majority of iris defects are not amenable to suture repair. "For them, they either limp along with tinted contact lenses, by patching the eye, squinting or closing the eye, or they have an artificial iris implanted," Dr. Miller explains.

Three different artificial irises are currently being marketed; however, only one, the CustomFlex Artificial Iris by HumanOptics, is currently approved for use by the U.S. Food and Drug Administration.

CustomFlex Artificial Iris

Approved in May 2018, the CustomFlex Artificial Iris is indicated to treat congenital aniridia, as well as iris defects caused by albinism, trauma or surgical removal due to melanoma.[1] It is made of thin, foldable silicone and is custom-sized and colored for every patient. To implant CustomFlex, the surgeon makes a small incision, inserts the device, unfolds it and smoothes out the edges. The device is held in place by the anatomical structures of the eye or by sutures, if necessary.

The CustomFlex was found to be safe and effective in a non-randomized clinical trial of 389 patients with aniridia or other iris defects. The study measured patients' self-reported decrease in severe sensitivity to light and glare after implantation of the device, increase in health-related quality of life and their satisfaction with their cosmetic appearance. More than 70 percent of patients reported significant decreases in light sensitivity and glare as well as an improvement in health-related quality of life. Additionally, 94 percent were satisfied with the appearance of the artificial iris.

Both the device and the surgical procedure had low rates of adverse events. Complications associated with the CustomFlex Artificial Iris included device movement or dislocation, strands of device fiber in the eye, increased intraocular pressure, iritis, synechiae, and the need for secondary surgery to reposition, remove or replace the device. Complications associated with the procedure included increased intraocular pressure, hyphema, cystoid macular edema, corneal swelling, iritis, retinal detachment and secondary surgical intervention.

The device shouldn't be implanted in patients with uncontrolled or severe uveitis, microphthalmos, untreated retinal detachment, untreated chronic glaucoma, cataract caused by rubella virus, rubeosis, certain kinds of damaged blood vessels in the retina, and intraocular infections. It is also contraindicated for pregnant women.

"It's a particularly unique device in that it can be placed either passively in the capsular bag for a patient who is having the procedure at the same time

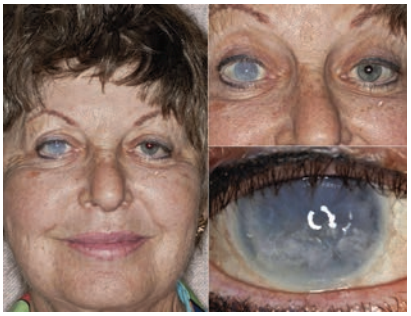


Figure 2A. This composite image shows the preoperative appearance of a woman who suffered from post-traumatic corneal failure, aphakia and complete aniridia.

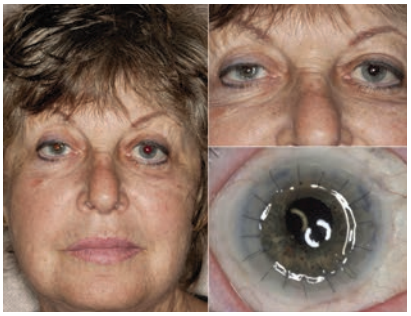


Figure 2B. This composite, three-month postoperative photograph shows the same patient after penetrating keratoplasty, anterior vitrectomy and scleral suture fixation of a HumanOptics artificial iris and posterior chamber IOL.

as cataract surgery, or it can be sutured to the eye wall in a patient who has no capsular structures and perhaps might require a sutured implant lens, for example," Dr. Snyder explains. "The device is custom made and matched to a picture taken of an uninjured eye in patients with a traumatic injury in one eye. A congenital aniridic can present a picture of an eye color that he or she likes. The picture gets sent off to Germany, the artificial iris is manufactured based on the picture, and then it's implanted in the eye. The matches are usually pretty realistic."

Dr. Miller notes that there is no standard surgery for implanting an artificial iris. "Ninety-five percent of the patients that I see with damaged irises are patients with trauma," he says. "Because of the nature of trauma, each eye looks different, so there's no standard surgery. The traumas tend to fall into four general categories: blunt trauma without globe rupture; blunt trauma with globe rupture; penetrating trauma; and surgical trauma. The last cause is actually pretty common."

He explains that the comorbidities of this group are diverse. Many of these patients have corneal scarring and corneal failure. "So, for those patients, we often perform a corneal transplant at the time of the artificial iris repair," Dr. Miller says. "Approximately 40 percent of patients will have glaucoma requiring some sort of medical or surgical management at the time that they undergo the iris repair. In terms of lens status, patients must have a cataract, a lens implant, or be aphakic at the time we manage the iris issue. We don't operate on eyes with clear crystalline lenses."

The approach to the iris portion of the procedure depends on everything else that is going on in the eye, Dr. Miller says. There are two different ways to place the artificial iris. In simpler cases, it can be injected through a lens-style injector system. In others, it can be placed with forceps, or it can be dropped in through a corneal transplant incision.

"How we fixate the iris also varies from eye to eye," he says. "If there's an intact capsule, it's sometimes possible to trephinate the iris and stick it inside the capsule. That's one way of passively placing the iris inside the eye. In some cases, we will place the iris passively in the ciliary sulcus if there's adequate capsule and zonular support to hold it there. And then, the other way to fixate the iris is to suture it to something, and there are many different suture techniques. We can suture the iris to the sclera; we can suture the iris to a lens implant, which is then sutured to the sclera; and we can suture the iris to residual iris tissue. The most common scenario is where we have to implant an iris and a lens at the same time. These eyes usually have no capsule and no zonular support, so we'll suture the lens implant to the back of the artificial iris and suture the artificial iris to the sclera. That's actually very common."

The Future

According to Dr. Miller, artificial irises provide a great cosmetic result. "In a patient who didn't have other obvious trauma, you probably wouldn't be able to tell that he or she had an artificial iris if you met him or her in a social situation," he says. "So, cosmetically, they're really good. However, many of us would love to see an integrated optic. The artificial iris is just a wafer-thin piece of silicone that rolls up, and it's got a fixed 3.35-mm pupil. It would be nice if we could pop a 22-D optic, or whatever power is necessary, inside the pupil and have it clip to the iris. Then, we wouldn't have to separately suture a lens implant to the back of the iris. So, that's a hope for a future development."

However, he notes that artificial iris implantation isn't common, so funds for clinical trials are scarce. "Those of us who brought the artificial iris to the market in the U.S. did it for free," Dr. Miller says. "Developing products and making improvements requires funds, and this company could never possibly fund a clinical trial. In the clinical trial we ran, the patients had to pay for the device, and it wasn't cheap. The surgeons performed the iris portion of the surgery for free. We would bill out whatever covered service we could. So, future developments will depend on another group of investigators willing to do the same." REVIEW

Dr. Snyder has a financial interest in HumanOptics and VEO Ophthalmics, and Dr. Miller has no relevant financial interests to disclose.

1. Artificial Iris approval notice. https://www.fda.gov/news-events/press-announcements/fda-approves-first-artificial-iris.

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Point-Counterpoint: Corneal Hysteresis and Glaucoma

Hysteresis Matters

John Berdahl, MD, Sioux Falls, S.D.

Ever since an ophthalmologist discovered that corneal thickness plays a role in glaucoma, we've been wondering about the role of biomechanics in this disease. Initially we thought that a patient with a thin cornea simply meant that we needed to adjust our IOP measurement to take corneal thickness into account. That's true, but it turns out that having a thin cornea is also an independent risk factor for progression of glaucoma. It's possible that a thin cornea is telling us something important about the biomechanics of the rest of the eye—especially the optic nerve head.

Measuring corneal hysteresis, or CH, is the next evolutionary step in the process of understanding this. CH is much more than a measure of thickness—it's a measure of the shock-absorbing capacity of the cornea, and hence, the shock-absorbing capacity of the eye. (A high level of hysteresis means the cornea has a large capacity for shock absorption; a low hysteresis indicates a cornea with little capacity to absorb shock.)

Hysteresis is calculated by measuring how the cornea deforms when pressure is applied and comparing that to how it returns to its normal shape. Reichert's Ocular Response Analyzer uses high-speed imaging of the cornea during the application of air puffs to measure these corneal changes. From that it deduces the shock-absorbing capability, or hysteresis, of the cornea.

"Measuring pressure in the context of CH has been a big win in our practice, so we use it for all of our patients."
- John Berdahl, MD

That corneal measurement may be telling us a lot about the shock-absorbing capacity of the optic nerve head—i.e., how much pressure the optic nerve head can tolerate. In fact, as the eye pressure goes up, the CH measurement goes down, which makes sense. The higher the pressure, the less shock-absorbing capability is left. It's like loading a pickup truck with 2,000 pounds of weight; the shock absorbers squeeze down, and then there's less shock-absorptive capability remaining. That's what happens to the cornea—and possibly the optic nerve as well—when IOP goes up.

Hysteresis and IOP

In our practice we rely primarily on the ORA instrument when we measure IOP, for several reasons. First, the IOP measurements are very accurate. In fact, I trust the CH-adjusted measurement more than the Goldmann measurement. If something isn't adding up, or we're making a surgical decision based on IOP, we'll measure the IOP in multiple ways, including Goldmann tonometry, but even in that situation I put most of the weight on the CH-adjusted pressure measurement.

A second reason we rely on the ORA's CH-adjusted IOP measurement is that the readings are easy to obtain, and they're user-independent. That helps us with our patient flow. Furthermore, there's no per-use charge, so it doesn't cost us anything to do it (other than our time). In terms of reimbursement for performing the measurement, we do submit it to insurance, but often insurance denies it. In that case, we pass the cost on to the patient. But even if we weren't charging anyone for it, I'd still use it.

Also, the CH-corrected IOP measurements are far less affected by

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Point-Counterpoint: Corneal Hysteresis and Glaucoma

Hysteresis Isn't Essential

Robert T. Chang, MD, Stanford, Calif.

There's increasing evidence in the published literature supporting corneal hysteresis (CH) as a risk factor associated with glaucoma and glaucoma progression. The Ocular Response Analyzer technology has been around for more than 15 years, and there are a few prospective longitudinal studies demonstrating benefit in glaucoma identification. However, when considering adding a significant capital expense with a modest, variable reimbursement, it's important to look at when the CH number is clinically useful and whether it will actually improve glaucoma management, given that CH isn't tracked or correlated with treatment success over time the way IOP or structural and functional optic nerve testing are.

At the moment, I don't think adding a CH value will change overall therapeutic decision making very often. Like central corneal thickness, it's merely a corneal behavior associated with glaucoma risk, mostly helpful in some glaucoma suspect cases.

"In most glaucoma cases, knowing the corneal hysteresis doesn't change our clinical decisions."
- Robert T. Chang, MD

Weighing the Pros and Cons

Here are some factors I'd consider before implementing corneal hysteresis as a regular part of my glaucoma protocol:

• ***In most glaucoma cases, knowing the corneal hysteresis doesn't change our clinical decisions.*** I view low corneal hysteresis as an additional risk factor for glaucoma, similar to having a thin cornea. If you measured CH in every glaucoma patient along with the rest of the complete eye exam, how many times would that change your clinical decision, especially after you've already initiated treatment? We currently use multiple known risk factors such as age, ethnicity, family history, CCT, IOP and optic nerve appearance. Without another prospective longitudinal study like the Ocular Hypertension Treatment Study, incorporating CH measurements along with known risk factors into a model designed to improve glaucoma risk assessment, we can't determine the added value this would provide.

Granted, we know that CH can help adjust IOP measurements post refractive surgery and that lower CH can be worse for glaucoma, including low-tension glaucoma. However, CH can also change with age and IOP variability. In fact, its repeatability is actually adversely affected by IOP. Thus, a low CH isn't good, but it's not really a treatable or progression-based endpoint.

• ***A CH-adjusted, "more accurate" IOP measurement may not be a game-changer.*** Because glaucoma worsening is often measured over longer intervals, collecting additional "less accurate" Goldmann applanation and other multiple IOP data points helps to overcome the issue of not knowing the "true IOP" within what is already a variable diurnal range. Thus, clinical decision-making and targeted IOP treatment ranges already incorporate this imprecision. Adapting to CH-adjusted IOP endpoints would require new clinical trials, especially since CH changes with IOP.

• ***Including one more risk factor generally doesn't change the bigger picture***. It's still not clear exactly why the association between

(Continued on page 67)

Hysteresis Matters
(Continued from page 64)

refractive surgery than Goldmann, since altered hysteresis after refractive surgery is a prime factor in altering Goldmann readings. The ORA measurement compensates for that. (It also gives you a second measurement that's an analog to a Goldmann measurement.) So we feel that we're measuring the true pressure inside the eye, as well as gaining insight into the biomechanical state of the eye.

Beyond IOP

Of course, there are other reasons we check CH when working with our glaucoma patients, beside getting an IOP measurement that I believe is more accurate. Several studies[1-4] have supported the usefulness of this for glaucoma management:

• ***Patients with a lower CH are more at risk of progression.*** An important study confirming this was done by Felipe Medieros, MD, at Duke University.[1] His prospective study showed that glaucoma patients with a lower CH—i.e., a lower ability to absorb the shock of increased IOP—progressed faster than patients with a higher CH, for a given level of IOP. So, if we find that a glaucoma patient has a low CH, we're going to be more aggressive about treatment. We may be more inclined to intervene with a MIGS procedure if we were undecided, and we may move to a trabeculectomy or tube shunt sooner.

• ***Patients with a lower CH are more likely to have undetected glaucoma.*** Because we measure CH in all of our patients, we decided to conduct a small study. We found that patients who came in with a lower CH had more advanced glaucoma—more visual field damage—on presentation than patients with a higher CH.[2] This indicated that their glaucoma wasn't detected as early as in patients at the same pressure who had a higher CH. To put it another way, having a low CH interfered with the timely detection of glaucoma. That is certainly useful clinical information.

A technician in Dr. Berdahl's office measures a patient's corneal hysteresis. Dr. Berdahl routinely measures hysteresis in all patients.

Measuring pressure in the context of CH has been a big win in our practice, so we use it for all of our patients. It reassures us that we're getting an accurate reading of the IOP, while providing other information that helps us manage our glaucoma patients more effectively. REVIEW

Dr. Berdahl is a corneal, refractive and glaucoma surgeon at Vance Thompson Vision in Sioux Falls, and associate clinical professor at the University of South Dakota. He reports no financial ties to any products discussed in this article.

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Hysteresis Isn't Essential
(Continued from page 65)

hysteresis and glaucoma exists, although some hypothesize that it relates to optic nerve head structural changes and susceptibility. Whatever the reason for that association, in most cases a single risk factor doesn't change our clinical decisions. If a glaucoma suspect's only risk factor is low CH, would you treat based only on that value? Unless there's a risk calculator incorporating CH, treatments can still be decided using structural and functional endpoints, along with CCT-adjusted IOP.

A Useful Tie-breaker

Of course, measuring corneal hysteresis can be helpful in some clinical situations. In particular, hysteresis becomes more valuable when other risk factors are uninterpretable or conflicting.

One longitudinal predictive study by Carolina Sussana, MD, et al., followed 278 glaucoma suspect eyes over four years.[1] It did produce a multivariable model adjusting for age, IOP, central corneal thickness, pattern standard deviation and treatment, and CH was still predictive of development of glaucoma (hazard ratio=1.20; 95% CI: 1.01–1.42; p=0.040). However, the confidence interval is close to borderline.

The Bottom Line

I don't see measuring corneal hysteresis as essential, because it has a narrow range of use. In my experience, the percentage of patients in whom this value will change my treatment decision is small. As a stand-alone risk factor, it doesn't have high sensitivity or specificity for diagnosing glaucoma, and it's not a factor that we can try to adjust to help the patient. Even its repeatability is affected by IOP.

Although the ORA has been around for a long time, it's still not common in all offices compared to OCTs and visual field machines. If it made a difference in the clinical realm for lots of patients, many more doctors would be using it. REVIEW

Dr. Chang is an associate professor of ophthalmology at Byers Eye Institute, Stanford University School of Medicine, in Stanford.

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(Continued from page 23)
in the presence of a retained nucleus can be critical because of the risk of a retinal detachment and the probability of needing a full vitrectomy."

In terms of retained cortical material that's not as dense and likely to dissolve upon observation, you can observe those patients closely, as long as you have a good view on a dilated exam, he adds. "But if you have any doubts, if you're not sure how dense the material is back there, you're always better off referring the patient and at least having the retinal specialist weigh in and decide whether or not it can be observed."

Dr. Lee cautions against taking risks as a result of a noble, but misguided, attempt to spare your patient a follow-up procedure after a ruptured capsule. "If you see material falling back into the eye, it's tempting to want to go back and get it," he notes. "But you can get into trouble by trying to do more than your training and equipment allow you to do. Once nuclear material gets fairly posterior, you're better off letting it go. Clean up the best you can anteriorly, put in a lens and leave the rest for the retinal surgeon."

"There's no downside to referring to a retinal specialist," adds Dr. Grayson. "Sometimes, you will think none of the nuclear fragments went into the posterior chamber, but the specialist will find a fragment down in the vitreous."

Quality Improvement

After a posterior chamber rupture, you may find it only natural to reflect and strive for improvement based on lessons learned. In an ideal world, Dr. Lee notes, you would record every posterior chamber rupture or other complication of cataract surgery on video. "You could review it, see what happened and try to figure out various things you might have done differently to get a better outcome," he says. "Because of that, I try to tape all of my high-risk cases. That's the ideal. But even if you don't have the complication on tape, it's important for your own development as a surgeon to think back later in the day, after you have finished surgery and everything is calmed down. Try to figure out what happened and what lessons you can learn."

Dr. Lee says he's learned something every time he's "broken a bag." He points out that surgeons are perfectionists. "We expect everyone to experience a great outcome," he says. "It's really hard on us when that doesn't happen. At the same time, you have to accept the disappointment and try to turn it into something positive, which is what you learn from the experience. You become a better surgeon after every case." REVIEW

Drs. Grayson and Wallace have no financial interest in the products discussed. Dr. Al-Mohtaseb has consulted for Alcon. Dr. Lee has consulted for J&J Surgical Vision and Alcon.

Non-IOL-based Presbyopia Treatments

Christopher Kent, Senior Editor

A number of approaches to relieving the symptoms of presbyopia are now in the pipeline.

The race to find a treatment for presbyopia—or at least its symptoms—continues unabated. Monovision, in which one eye is given a distance focus and the fellow eye a slightly nearer focus, has been a popular way to address this for many years. That's been true in part because the alternatives (multifocal intraocular lenses, for example) can have drawbacks such as glare and haloes that not all patients are willing to tolerate, in addition to being considerably more expensive. But monovision also has drawbacks, notably the loss of summation between the two eyes, limiting how much difference can be created. Nevertheless, several of the newer options profiled below take advantage of monovision to extend the vision range their approach provides.

Here, we'll review 11 options that are attempting to treat the limited vision caused by presbyopia without resorting to implanting a multifocal IOL. They can be thought of as falling into three categories: 1) pharmaceuticals that use miosis to take advantage of the pinhole effect; 2) surgical approaches; and 3) pharmaceutically altering the crystalline lens or cornea.

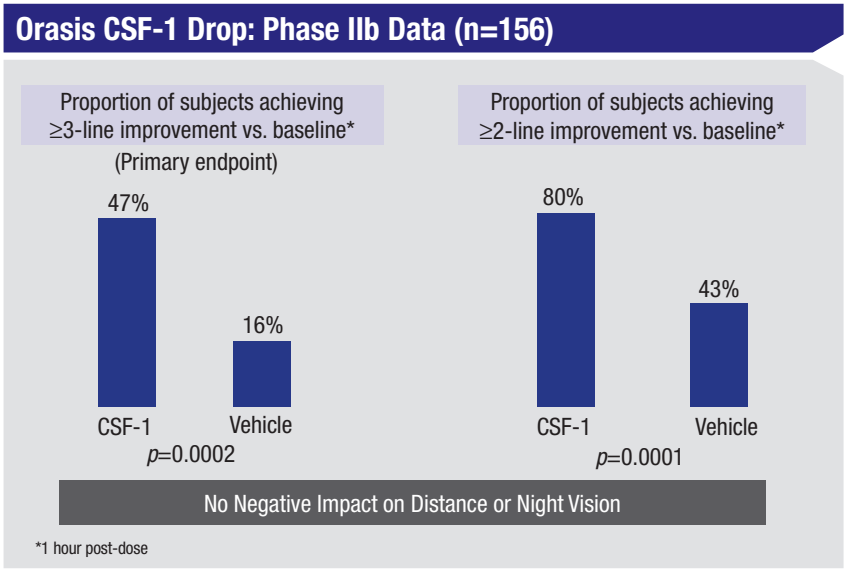
Pharmaceutical Miosis

One of the most intriguing avenues of research into presbyopia correction involves the use of topical drops to alter the pupil in order to confer near vision. Here's the latest:

• ***The Orasis Drop.*** An eye drop designed to relieve symptoms of presbyopia using miosis is being developed at Orasis, a company based in Israel. Asked what makes the Orasis drop innovative, CEO Elad Kedar says that one of the keys is finding the miosis "sweet spot." "You need to constrict the pupil just the right amount," he explains. "If you constrict the pupil too much, it can have a negative impact on distance vision, night vision and visual field, among other things. So the key is to find the amount of miosis that will give the person great visual acuity without causing any negative phenomena. And of course, the drop has to avoid causing adverse events such as headache, brow ache and red eye. This is especially important in a quality-of-life drug; there can be no compromise on safety and tolerability in this situation.

"The three key elements we see as essential are efficacy, safety and comfort," he continues. "We want people to be able to use our drug on a daily basis. We want the drop to be comfortable when they administer it, we want them to have freedom to

This article has no commercial sponsorship.



choose when to use it, and finally, we want the drop to start working fast and last a good length of time. So far, the data from our studies show that we've reached that optimal balance. Furthermore, this is intended for use in both eyes."

Mr. Kedar notes that the active ingredient in the drop is low-dose pilocarpine. "We're using a concentration significantly lower than that used with glaucoma," he says. "Also, our drug has a multifaceted vehicle that works with the pilocarpine to create that optimal balance of efficacy, safety and comfort. The onset of action is rapid; studies so far show significant results after 20 minutes. In terms of duration, the effects are still significant after several hours. For some people, especially younger people, it could last even longer.

"We're aware of what competitors are working on, and our drop is definitely different from theirs in a number of respects," he adds.

Asked about downsides to the drop, Mr. Kedar says they've worked hard to ensure there wouldn't be any. "This is a temporary, noninvasive way to address presbyopia," he points out. "Some people will use it every day, others will only use it occasionally. We're not trying to eliminate reading glasses. We're trying to provide freedom of choice and a great temporary solution that doctors can offer their patients, benefiting both parties."

Mr. Kedar says the company completed a Phase IIb multicenter, double-masked clinical trial involving 166 participants in 2019. "We met the primary endpoint successfully," he notes. "Participants gained at least three lines of improvement at near and the data showed no reduction in distance vision or night/low-light vision, which is a key element of efficacy. In fact, the data showed a trend toward improved distance vision. All of the safety and tolerability endpoints were met, as well. That's allowing us to go directly into a Phase III trial, which should be starting soon."

Mr. Kedar adds that they recently completed Series C funding that raised $30 million to advance Orasis' lead eye drop candidate through completion of its Phase III clinical trials, and for pre-commercialization activities ahead of a potential product launch.

• ***Liquid Vision.*** Presbyopia Therapies, a company based in Coronado, California, has developed a drop called LiquidVision that creates miosis without inducing myopia, to address the symptoms of presbyopia. Unlike some other presbyopia drops that use pilocarpine, LiquidVision's active ingredient is aceclidine, which has a different mechanism of action that the company says produces a greater depth of field than pilocarpine. Data from the company-sponsored Phase IIb study showed that this drug produced a pupil size ranging from 1.5 mm to 2 mm, without inducing any blurring at distance. The company says the drop allows patients to see both near and far simultaneously, from 16 inches to infinity.

Jim McCollum, CEO of Presbyopia Therapies, explains that aceclidine's MOA should make it possible to treat the symptoms of presbyopia in a wider age range and broader refractive error range than pilocarpine. "LiquidVision can treat symptoms in people from ages 45 to 70, with between -4.5 and +1.5 D of spherical error and up to 2 D of astigmatism," he says. "That's 80 percent of the bell-shaped curve. Pilocarpine-based drugs may work fine, but they'll work for a much narrower group of patients and will likely be more of a niche product.

"Both pilocarpine and aceclidine have been in use for 40 or 50 years, so they have massive amounts of safety data," he continues. "Aceclidine, by its nature, is temporary and reversible. In the Phase IIb study, some patients saw well for eight hours with one dose. Some patients may use it once a day, but the FDA label will most likely be for b.i.d. dosing."

Mr. McCollum notes that the data hasn't revealed any significant change in night vision/low-luminance conditions. "Good night vision is an important regulatory and commercial endpoint," he says. "Some patients may choose to use the drug at night because it filters out glare and haloes, and the data show no loss of vision at night. If you're trying to read a menu

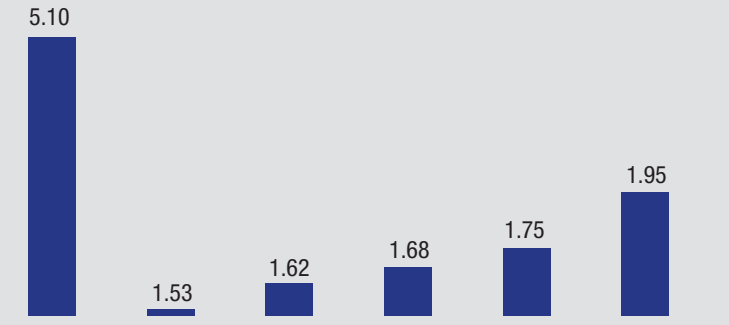
in a candlelit restaurant, you might be challenged, but if you're just functioning normally, for example, driving at night, you shouldn't have issues. Incidentally, when you sleep at night, the drug washes out, and by morning, you're back to your original baseline. We consider that a safety component of the drug."

Mr. McCollum says the drop might be contraindicated in patients who have had some types of retinal surgery or have an early cataract, which would limit its efficacy. "We expect that interested patients could sample it in a doctor's office," he says. "It only takes 20 to 25 minutes to act, so you can tell very quickly if a given patient is getting a good response."

Mr. McCollum says the Phase II trial has been completed, with a Phase III trial expected to begin in 2021.

LiquidVision: Mean Pupil Size (mm) in Phase IIb Trial

Pupil miosis 1.5 to 1.9 mm with strong biomarker correlating with time point near vision



	Predose	1 hour	3 hours	4 hours	5 hours	7 hours
≥ 2 line		92%	69%	69%	44%	44%
≥ 3 line		47%	31%	28%	22%	14%

Note: All *p*-values <0.001

• ***Allergan/Abbvie's AGN 190-584 Drop.*** Another entry in the competition to create an ideal topical presbyopia drop is Allergan's AGN 190-584. "AGN-190584 is an experimental formulation of pilocarpine, a cholinergic muscarinic receptor agonist, that's being investigated for presbyopic near vision correction," explains Michael R. Robinson, MD, vice president and global therapeutic area head of ophthalmology at Allergan. "This will be a topical, once-daily drop delivered by a proprietary vehicle."

Initial studies tested pilocarpine in tandem with oxymetazoline, a direct-acting alpha-1 adrenergic agonist and alpha-2a adrenergic partial agonist. Data from the company's Phase IIb study involving 151 individuals, meant to determine the efficacy of different formulations of the drop, were recently presented at the annual American Academy of Optometry meeting.

Subjects were divided into five groups; one served as the control, while the others received different combinations and strengths of the two key drugs. All participants received one drop per day for 28 days. Results included:

• Improvements in vision were seen within 15 minutes in all groups; peak improvement was seen at one hour. Vision continued to improve from day one to day 21, and was maintained at day 28.

• In the groups receiving stronger doses, gain in mesopic UNVA at day 28 ranged from 7.54 to 7.81 letters.

• All treatment groups demonstrated efficacy compared to vehicle, and there was no sign of tachyphylaxis during the 28-day dosing period.

• Headache was the most common adverse event, reported by 16.7 percent to 28.1 percent of the different treatment groups. (Notably, 10.7 percent of the control group members also reported experiencing headache.)

Phase III studies of the latest formulation—GEMINI I and GEMINI II—are currently ongoing.

• ***Brimochol.*** Another potential treatment for the symptoms of presbyopia is under investigation by Visus Therapeutics (Irvine, California). Their drop combines two active ingredients: carbachol and brimonidine tartrate. According to the company, five clinical studies have already been conducted. The most recent study involved 57 patients, and showed a near-vision improvement of five lines or more (a statistically significant difference) that lasted at least 12 hours. Participants reported no headaches or brow aches.

The company recently formed a clinical advisory board headed by Eric Donnenfeld, MD, joined by a number of high-profile ophthalmologists including Ed Holland, MD, Marguerite McDonald, MD, FACS, William Trattler, MD, and George Waring IV, MD, FACS.

Phase II trials are expected to begin in 2021.

• ***FOV Tears.*** An eye drop developed by Colombian ophthalmologist Luis Felipe Vejarano, MD, is showing promise as a treatment for the symptoms of presbyopia. The drop is intended to create what Dr. Vejarano calls "dynamic pseudoaccommodation," which combines a small amount of miosis with improved accommodation. Early studies showed that the drop doesn't impact distance vision.

The drop, which contains pilocarpine and several other components,

can be used bilaterally. Onset of action and duration of effect apparently improve with long term use; onset takes five to 10 minutes for most users by the third month of use. The effect lasts four to five hours at first, but may last up to eight hours after extended use. Most patients have been using the drops two times a day, once in the morning and once around mid-afternoon. Some patients also use a third drop in the evening, depending on their vision needs.

Several studies have been published, the most recent in 2019.[1] In that prospective, interventional, non-comparative study, 117 presbyopic patients were given one drop in each eye. Patients were divided into two groups: age 41 to 50 years old, and age 51 to 65 years old. Two hours after instillation of the drops their binocular uncorrected near visual acuity (UNVA) and uncorrected distance visual acuity were evaluated. Researchers also assessed subjects' objective scatter index and pupil diameter under photopic and scotopic conditions, before and after instillation.

Findings included:

- The mean UNVA before instillation was 0.35 logMAR (20/45). At two hours after instillation, logMAR improved to 0.16 (20/29).
- Near vision improved by at least one line in 92.3 percent of the patients at two hours.
- Nine patients (7.6 percent) failed to show an improvement.
- No patients lost any lines.
- Fourteen patients (11.9 percent) reported experiencing headaches.
- The younger age group gained more lines than the older group.

Jorge L. Alió, MD, PhD, a professor and Chairman of Ophthalmology at the University Miguel Hernandez de Elche, in Alicante, Spain, has conducted several clinical trials using the drops. (He has no financial ties to the drops.) "Our first pilot study showed that the drop made a significant difference in patients with early or intermediate presbyopia," Dr. Alió explains. "It even worked in presbyopes with previous refractive surgery, whether intraocular or cornea-based, including patients who had undergone presby-LASIK."

Dr. Alió notes that FOV Tears don't work equally well in all presbyopes. "In our studies, about 70 percent of the patients gave a positive evaluation of the medication. However, about 30 percent were either not improved—possibly because their presbyopia was too advanced—or they had some minor side effects that discouraged them from using the medication," he says. "In my experience, this formula is effective in all patients with early or intermediate presbyopia, eliminating the need for reading glasses. Once we know which are the best cases to treat, I think this will be successful in more than 90 percent of patients.

"My wife has been using these drops for almost three years," he adds. "She's happy and doesn't need any other solution for her presbyopia."

FOV Tears have been approved for use in Spain, but are not currently available in the United States.

Surgical Approaches

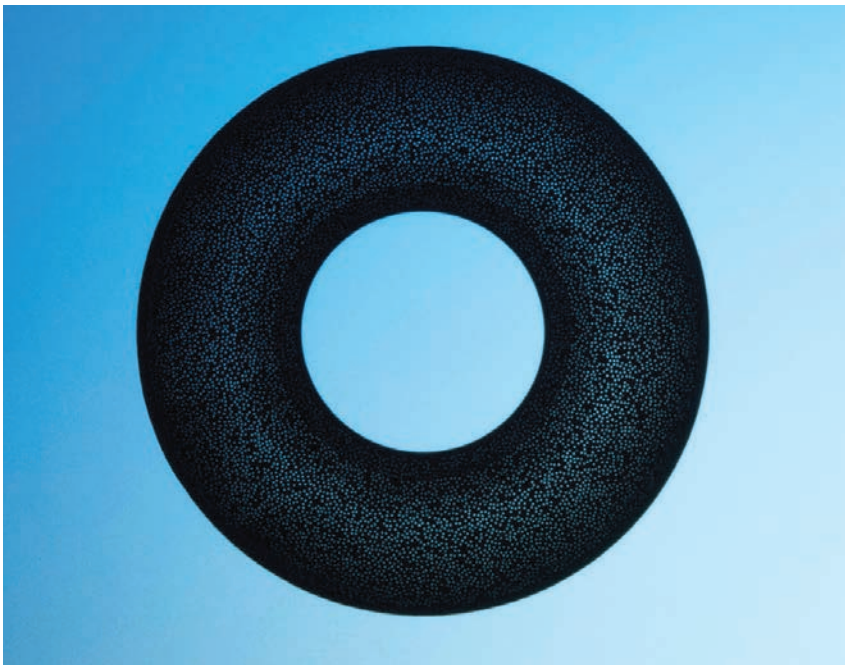
Here's an update on more invasive methods for treating presbyopia, some of which have been in the works for a while:

- ***KAMRA.*** Several corneal inlays have been developed over the years, hoping to improve the range of vision in presbyopes, but only one is currently available: the KAMRA inlay (initially brought to the marketplace by AcuFocus, now available from SightLife Surgical/CorneaGen).

The 5 µm thick, 3.8-mm diameter polyvinylidene fluoride device features a 1.6-mm central aperture; it uses the pinhole principle to improve range of vision. The device has more than

8,000 microperforations of different sizes designed to allow oxygen and nutrients to pass through. It's implanted in a 200-µm deep femtosecond-laser-created pocket in the cornea of the non-dominant eye. To work effectively, vision should be between -1 and plano before the surgery, which can be accomplished via LASIK in a separate procedure, if necessary.

Although surgeons agree that the device is effective, the KAMRA inlay hasn't swept the presbyopia market. That may be because A) most people don't know someone else who's already had one implanted; B) it requires adjusting to some degree of monovision, since it's meant to be implanted only in one eye; C) it may require an additional procedure to get the patient to emmetropia before implantation; and D) it's not inexpensive. Nevertheless, it a valuable option to offer patients—and unlike many presbyopia options in development, it's available now.



The KAMRA inlay uses the pinhole principle to achieve a range of vision.

• ***The PEARL Procedure.*** In addition to pharmaceutical options, doctors are still investigating surgical ways to alter the cornea and improve vision once presbyopia begins limiting patients' range of vision.

One novel approach developed by Soosan Jacob, MS, FRCS, DNB, director and chief at Dr. Agarwal's Refractive and Cornea Foundation in Chennai, India, uses a biological tissue implant (rather than a synthetic implant) to create a hyperprolate central cornea that improves near and distance vision. The procedure, known as PEARL (PrEsbyopic Allogenic Refractive Lenticule), places a tissue lenticule—sometimes harvested from a SMILE procedure done on another eye and trephined to form a 1-mm disc—into a 120-µm-deep femtosecond laser-created corneal pocket. Using a tissue implant avoids the problems that can be associated with a synthetic implant, such as corneal melt, fibrosis, opacification and haze. After healing, the implant is invisible, and it's permeable to oxygen and nutrients moving through the cornea. (You can watch a video of the procedure at youtube.com/watch?v=8H4Ns1b8L3M&ab_channel=Dr.SoosanJacob.)

"I realized there are many issues with putting synthetic implants in the cornea," says Dr. Jacob. "They were giving good results, and people were happy with the vision they gained, but the cornea never tolerates a synthetic implant very well. I wanted to find a way to provide the advantages of this approach without the complications. That's when it struck me that if we could do the same thing using biological tissue, these issues might not arise. In fact, that has turned out to be correct."

Dr. Jacob points out that the tissue doesn't have to come from a SMILE procedure. "PEARL can be done using any allogenic tissue, processed or unprocessed," she explains. "Just as LASIK encompasses various different types of ablation profiles and machines, PEARL is similarly an all-encompassing term. We had SMILE tissue available when developing the procedure, so we used that. However, one can use tissue from any source to perform PEARL. In fact, I'm now developing another technique using allogenic tissue to address keratoconus and ectasia, called CAIRS (Corneal Allogenic Intrastromal Ring Segments)."

Dr. Jacob notes that in comparison to some surgical techniques, such as a corneal surface ablation, PEARL is reversible. "Also, it's an additive procedure, not a subtractive procedure like LASIK," she says. "In addition, PEARL doesn't have contraindications such as a thin cornea.

"Of course, no presbyopic solution is perfect," she adds. "PEARL can cause a slight drop in distance visual acuity, so it's only done in the non-dominant eye; that way, binocular vision remains good for both distance and near. Patients who might not be good candidates for PEARL would include patients with lens changes, those unwilling to accept a slight drop in distance vision in the operated eye, patients with unrealistic expectations, and patients with systemic or ocular

diseases. In terms of possible complications, the cornea could theoretically reject the implant, but we haven't seen this in our series of cases. Reasons for the low risk of rejection are many, including the position of the implant, the sequestered location and the small volume of tissue used, among others."

• ***Supracor.*** Another approach to overcoming the vision limits associated with presbyopia has been using laser ablation to create a multifocal cornea. One current technique for doing this is the Supracor treatment developed by Bausch + Lomb and manufactured by Technolas Perfect Vision (not currently approved in the United States). The procedure is performed on the Technolas TENEO 317 Model 2 excimer laser (also not available in the United States). Robert E. Ang, MD, a senior consultant at Asian Eye Institute in Makati City, Philippines, and an investigator for Bausch Health Companies, is well-acquainted with the procedure.

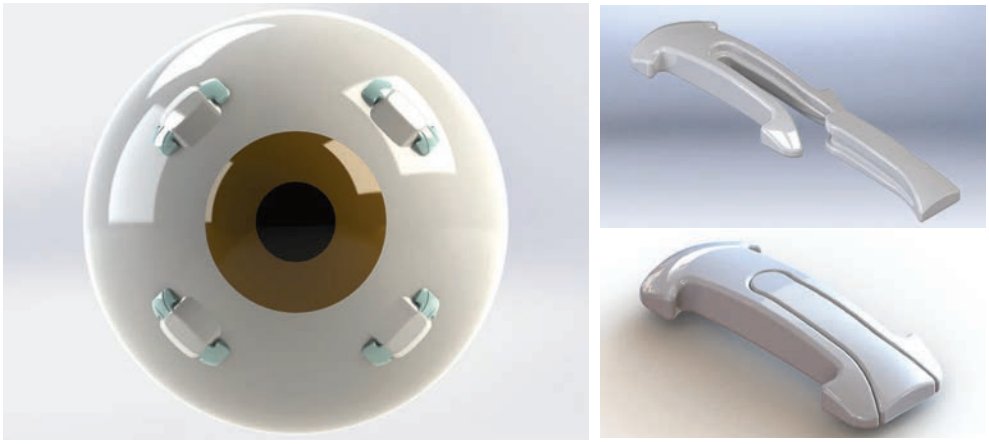
"Supracor creates a varifocal cornea," he explains. "Negative spherical aberration is fashioned in the central 2 mm for near vision, and an aberration-optimized zone is created in the mid-periphery to allow good distance vision. This treatment profile provides approximately 1.5 D of reading add, but since the target refraction is -0.5 D, the result is a total reading add of about 2 D. When a refraction of -0.5 D is achieved, both mean uncorrected near and distance vision are 20/25. Six year data on Supracor treatments for hyperopes and myopes have confirmed this, with a mean MRSE of -0.52 D for hyperopes, and a mean MRSE of -0.45 D for myopes."

Dr. Ang notes that Supracor is similar to other corneal presbyopia treatments in that it uses the excimer laser to manipulate spherical aberration. "Supracor alters the spherical aberration in the central 2 mm of the cornea," he says. "By using the center-near, periphery-distance approach, Supracor makes use of pupil dynamics during accommodation, as the pupil constricts when reading and dilates when looking at distant objects. The main difference between Supracor and other corneal ablation approaches is the proprietary Supracor algorithm that determines the amount of aberration change centrally and the optimization of the mid-periphery. The algorithm ensures that distance vision isn't significantly affected."

Dr. Ang explains that Supracor is a successor to the IntraCor femtosecond laser procedure. "In IntraCor, five concentric rings were created in the corneal center," he says. "The rings induced negative spherical aberration through a controlled curvature change and steepening of the central cornea. IntraCor topographies were analyzed and recreated using excimer laser treatment on the stromal bed. Supracor LASIK was found to be better than IntraCor because the excimer laser is very precise in correcting refractive error, targeting a desired refractive outcome and creating a desired corneal shape."

Dr. Ang points out that Supracor has three different modes: mild; regular; and strong. "To balance distance and near vision and conform to a patient's needs and expectations, surgeons can choose to utilize a modified monovision approach," he says. "For example, you might choose to use Supracor mild in the dominant eye and Supracor regular in the non-dominant eye. Or, you could perform standard LASIK in the dominant eye and Supracor strong in the non-dominant eye."

To ensure a good outcome, Dr. Ang says surgeons have to be careful to center the treatment at the visual axis. "If the treatment isn't centered, the result can be significant coma, leading to distorted vision and an unhappy patient," he says. "It's also crucial to evaluate patient acceptance and manage expectations when selecting patients. Patients have to understand



The VisAbility Micro-Insert (Refocus Group) uses implants placed in the four quadrants in the sclera to alter the spacing between the gradually enlarging crystalline lens and the ciliary muscles, thus improving accommodation, according to the company.

that distance vision after Supracor will probably not be as sharp, which would not be the case with standard, non-presbyopic LASIK."

In terms of contraindications, Dr. Ang says standard LASIK criteria apply, such as leaving a residual stromal thickness of at least 250 µm and excluding corneas that might have forme fruste keratoconus. "There's an additional exclusion criterion that applies to hyperopes," he notes. "If the projected keratometry after Supracor will go beyond 48 D, the patient has to be disqualified because overly steep corneas produce poor outcomes."

Bausch + Lomb is not currently planning to seek approval for Supracor in the United States.

• ***VisAbility Micro-Insert.*** Among the surgical options that may help to address the symptoms of presbyopia is the VisAbility Micro-Insert system (Refocus Group, Aliso Viejo, California). This system consists of four 5-mm-long micro-thin polymethylmethacrylate (PMMA) scleral implants, each smaller than a grain of rice. The implants are placed just below the surface of the sclera about 4 mm from the limbus in the four quadrants of both eyes using a specially modified sclerotome to ensure uniformity. (*See illustration above.*) Each implant has two parts; the second, smaller part locks the first part in place inside the scleral tunnel.

The procedure's mode of action is based on the theory that a key cause of presbyopia is the gradual enlargement of the lens, leading to decreasing space between the lens and the ciliary muscle.[2] The VisAbility system is intended to adjust the tension of the posterior zonules, which connect the lens to the ciliary body, thus restoring some amount of accommodation. Placing the implants is an outpatient procedure done under topical anesthesia. Once in place, the company says the implants aren't felt by the patient or visible to others under normal gaze.

In the initial study, 330 presbyopic subjects age 50 to 60 had the procedure in the primary eye, followed by surgery in the fellow eye at least 14 days later. The primary endpoint was to have at least 75 percent of patients achieve binocular 20/40 (or J3) DCNVA at 40 cm by the end of the study. At one year, 94 percent had achieved this, and DCNVA continued to improve during three years post-surgery. At the 2017 meeting of the American Academy of Ophthalmology, James Katz, MD, reported data from 177 participants who were followed-up for 36 months. Ninety-five percent of subjects had achieved the endpoint by 24 months; the percentage achieving this rose to 97 percent at 36 months.

Most potential downsides associated with the procedure appear to relate to healing and potential pain from the scleral surgery.[2]

A follow-up study is currently under way to obtain an additional 36 months of safety and effectiveness data from subjects implanted with the inserts during the previous trial. The company hopes to complete this trial by July 2021. The VisAbility Micro-Insert system is currently under FDA consideration.

Altering the Lens or Cornea With Pharmaceuticals

While some novel pharmaceutical options for presbyopia focus on the pupil, others take a different route: the crystalline lens or the cornea. Here's an update on their status.

• ***Novartis' UNR844 Drop.*** Researchers have long noted that presbyopia appears to result from multiple factors, one of which is reduced crystalline lens flexibility with aging. Evidence suggests that our lenses gradually oxidize, causing disulfide bonds to form. These disulfide bonds restrict the lens's ability to change shape in response to ciliary muscle contraction and relaxation, and they contribute to the development of nuclear sclerotic cataracts. Thus, one potential approach to treating presbyopia is chemically reducing disulfide bonds in the lens.

A topical agent from Novartis, referred to as UNR844, uses lipoic acid choline ester to do exactly that. The

drug is formulated as a prodrug that improves its penetration through the cornea. The drop is intended for bilateral use.

The company's prospective, randomized, double-masked, placebo-controlled Phase I/II study enlisted 75 patients age 45 to 55 years with a diagnosis of presbyopia. At baseline, participants' distance-corrected near vision was below 20/40 in both eyes. Fifty patients received UNR844; 25 received placebo. Patients received drops for 91 days and were then monitored for seven months. Findings included:

- Bilaterally, 84 percent of patients receiving UNR844 improved to 20/40 or better, versus 52 percent of those receiving placebo.
- Fifty-three percent of those receiving UNR844 experienced an improvement of at least 0.2 logMAR; only 22 percent receiving placebo achieved this.
- The drug caused no change in visual acuity, manifest spherical equivalent or pupil diameter.
- Seven months after study completion, 39 percent of treated subjects maintained their improvement in bilateral vision, compared to only 6 percent of the placebo group.
- No subjects discontinued.

"One of the advantages of this approach to treating presbyopia is that its mechanism of action directly addresses the cause of presbyopia and nuclear sclerotic cataract," says Michael Korenfeld, MD, an associate clinical professor at Washington University School of Medicine, and a principal investigator and paid consultant for Novartis. "Currently, we don't know how much restoration of function can be accomplished with this drug. The recent study included a small cohort of humans dosed for 90 days. In theory, it might be possible to achieve total restoration of accommodative function with longer durations of treatment or more frequent intervals of dosing, but at this point we simply don't know."

Dr. Korenfeld notes that there's some debate about whether addressing the root cause of presbyopia is a better approach than relieving symptoms temporarily. "The effects of this drug last a long time," he points out. "Some companies are developing drugs that make the pupil smaller for less than a day. They see being able to turn near vision improvement on and off as a benefit. Others think that reversing the underlying pathology and having a lasting and continuous benefit is more advantageous." (Of course, UNR844 only works if the patient still has his natural lens; a pupil-based solution doesn't have that limitation.)

Dr. Korenfeld says that, with the exception of pseudophakic patients, he sees no obvious reason this couldn't be tried on any presbyopic patient. "Novartis is actively working to develop this drug," he notes. "At this point it's impossible to say when it might reach the marketplace, but it will probably be within a few years."

• ***Yolia True Vision***. Another approach to addressing the limited vision caused by presbyopia, using a system originally developed in Mexico by the late Alberto Osio Sancho, MD, and later incubated at Johnson & Johnson Labs, is now available in Mexico from Yolia Health. According to Alberto Osio, CEO of Yolia Health, True Vision is a non-invasive, repeatable treatment involving patient self-administration of proprietary enzyme eye drops that increase corneal malleability, followed by wearing individually customized contact lenses that reshape the cornea's sphericity to produce multifocal vision. (TVT is approved by the Mexican FDA; it's part of Yolia Health's "Invisalign" platform of treatments using the same premise to correct a range of vision problems including myopia, hyperopia, digital fatigue and post-surgery refractive errors.)

Patients use the TVT system for a week; the company says that the resulting vision change can last for up to a year before retreatment is needed. It's designed to be used in both eyes, improving near vision without compromising distance vision. According to the company, after using TVT, 92 percent of patients can read newsprint, with a near-vision gain of up to five lines lasting more than eight months, and 91 percent report improved distance vision as well. TVT can be repeated as needed, and the reshaping can be modified over time as the eyes change. The company reports no adverse effects associated with the treatment.

A small study sponsored by Yolia enrolled 50 patients between the ages of 40 and 60. Participants were screened for dry-eye disease and their vision and anterior segments were assessed; then contacts lenses were prepared and TVT kits were distributed to each subject. Findings included:

- At day eight, uncorrected near visual acuity was significantly improved in all eyes ($p<0.01$), with an average near gain of more than two lines.
- Seventy percent of patients had an improvement of two lines, almost half had an improvement of three lines, and 23 percent had an improvement of four or more lines.
- Uncorrected distance acuity also improved an average of one line by day eight ($p<0.01$).
- These improvements were stable from day eight to day 180.

More than 600 patients, including 55 international patients, have been treated with the TVT system. TVT has been submitted to the FDA, and the company hopes to receive approval by 2023. REVIEW

1. Vargas V, Vejarano F, Alió JL. Near vision improvement with the use of a new topical compound for presbyopia correction: A prospective, consecutive interventional non-comparative clinical study. Ophth and Therapy 2019;8:31-39.
2. Baitch L, Schanzlin D, Iskander D. One-year post-operative wavefront and refractive map changes following scleral implant surgery. Presented at the 15th International Congress on Wavefront & Presbyopic Refractive Correction, 2014; Dana Point, California.

How to Handle Dislocated IOLs

Michelle Stephenson, Contributing Editor

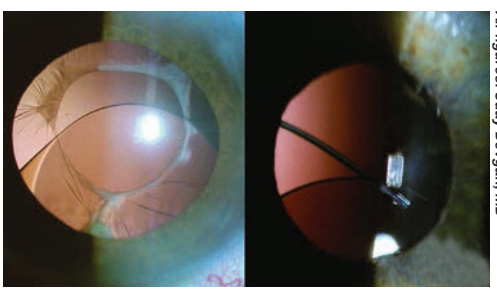
Experts review the salient points regarding repositioning and fixating intraocular lenses that refuse to cooperate.

Surgeons say that even though intraocular lens dislocation at the time of surgery is rare, that's all the more reason to keep your management skills for this particular complication sharp. Unfortunately, there's no surefire technique for handling IOLs that won't fixate properly, so surgeons have to use one that's most comfortable for them, as well as be aware of the other options in case one of them turns out to be ideal for a particular situation. Here, cataract experts share their advice on handling these cases.

Common Causes

"Dislocation is often due to progressive zonulysis, and certain conditions predispose to that eventuality, most typically pseudoexfoliation," says Samuel Masket, MD, in practice in Los Angeles. "However, an increasingly common etiology for late decentration of the capsule bag IOL complex is pars plana vitrectomy, either because of removal of posterior zonular fibers and/or a chronic breakdown of the blood-aqueous barrier. In fact, any condition that has a breakdown of the blood-aqueous barrier is likely to be associated with a progressive zonulysis.

Uday Devgan, MD, also from Los Angeles, says he considers the following in these cases: "How dislocated is the lens?" he asks. "Also, does it fall back into the vitreous when the patient lies supine? Should the current lens be kept or replaced? And, if the current lens is to be retained, how can it be secured?"



All figures: Uday Devgan, MD

Figure 1. These dislocated IOLs are just behind the iris and aren't entwined with vitreous. The single-piece IOL (left) offers fewer options for fixation compared to the three-piece IOL (right), say surgeons.

Keep or Replace the Lens?

Dr. Devgan says that surgeons may want to keep the current lens if the patient has done well until the dislocation. However, if the lens is damaged, then it makes sense to exchange it. "When suturing a lens to the sclera or iris, it's difficult to perfectly center the lens or align it with a toric axis. Therefore, for toric or multifocal lenses, it's probably best to remove the lens and implant a standard monofocal lens, because monofocal lenses are more forgiving in terms of decentration or rotation," he says.

According to Dr. Masket, the ideal approach is to keep the IOL inside the eye and fixate it in some fashion.

This article has no commercial sponsorship.

"Among the skills that the surgeon needs to have available is an ability to re-open the capsular bag if the IOL needs to come out and the ability to stabilize or capture the IOL or IOL-bag complex by going behind it. This is done using the pars plana approach or by placing a safety basket suture, kind of like a tic-tac-toe board of 10-0 polypropylene as a safety net placed underneath," he explains.

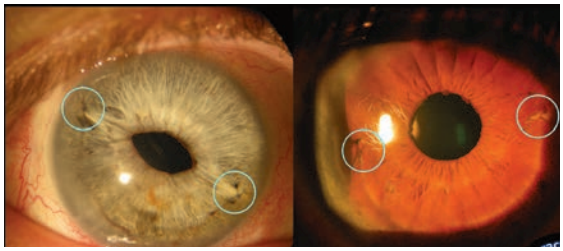


Figure 2. Suturing the haptics of a three-piece IOL to the iris can provide a good degree of optic stability, surgeons say. The ovoid pupil shape (left) can be avoided by pulling the iris tissue centrally prior to cinching down the suture knots.

Securing the IOL

Dr. Devgan notes that IOLs are typically secured to the sclera or the iris. "If there is absolutely no capsular bag support, suturing the IOL to the iris is probably not a good choice," he says. "It will probably need to be fixated to the sclera. If you choose iris fixation, the lens itself will be a big weight on the iris, and if there's no capsule or any other tissue back there, the lens can shake too much and may eventually break off. With the sclera, there are many fixation options. IOLs can be sewn in or glued in, or we can use the Yamane technique."

For suturing a haptic to the iris, Dr. Devgan uses 10-0 prolene. "This is a good choice because it will last and it's in a protected space," he says. "If you're sewing an IOL to the sclera, there are two options: You can fixate the haptics themselves to the sclera using either the glued IOL technique where you make small tunnels; or you can use the Yamane technique in which you use a cautery to burn the end of the haptic to create a little bulb so it doesn't move. I tend to use Gore-Tex if I'm going to suture a lens to the sclera. It works really well and has great long-term stability. It's important to note that sewing a lens to the iris using the Yamane technique or the glued technique is off-label, and certainly using the Gore-Tex is off-label."

An on-label option is to remove the dislocated lens and implant an A/C IOL. "A lot of these complex techniques aren't easy, but placing an anterior chamber lens is relatively easy," Dr. Devgan says. "Some surgeons recommend sewing a lens in, and they don't ever implant an anterior chamber lens. However, studies have shown that anterior chamber lenses that are well-placed perform about the same as any of the suture-fixated lenses."

Lance Ferguson, MD, from Lexington, Kentucky, considers the IOL material and the amount of scar tissue when planning his approach. "For dislocated but capsular-fixated IOLs, regardless of material, I can secure the IOL-capsule complex by encircling the haptic with a double-armed Gore-Tex suture placed at the haptic-optic junction and then fixate through the scleral wall. If the IOL is scarred down in the bag, then posterior support with a vitrector via a pars plana approach may be required to stabilize the IOL while driving the needle through the complex.

"If the dislocation is relatively recent with respect to the initial cataract surgery," he continues, "then I viscodissect the IOL from the capsule, place a Cionni Ring or Ahmed segment, and recenter the bag by suturing it to the sclera, again with Gore-Tex. Another approach is to free the IOL from the bag, place it in the sulcus, and then suture to the iris with prolene. This works only for a three-piece IOL. Acrylic one-piece IOLs shouldn't be placed in the sulcus or sewn to the iris. They should be partially bisected and removed in one piece."

Dr. Ferguson also considers general anesthesia if the patient's health doesn't preclude it. If a patient is very old and won't be able to withstand general anesthesia well, Dr. Ferguson recommends using an anterior chamber lens, remembering to perform a peripheral iridotomy at the end of the surgery. "This is for patients with a solid endothelial cell count," he says. "It's not ideal, but it may be the best solution for a very feeble individual who can't undergo general anesthesia well or won't be able to cooperate well during surgery."

Santa Clara, California's Huck Holz, MD, agrees that the type of lens is a consideration. "If it's a three-piece IOL in the bag and it's not completely dislocated, then I use a lasso suture. I have started using 8-0 Gore-Tex suture that I load into the lumen of a 30-gauge TSK large-bore needle, and I just thread it in. I then pass the loaded TSK needle 2.5-mm posterior to the limbus and underneath the haptic. I then retrieve the end of the suture through a sclerotomy located 0.5-mm anterior to my original needle entry with a microforceps. The other haptic is addressed in similar fashion. The suture is then tied and trimmed, and the knot is buried into the sclerotomy," he says.

For one-piece IOLs that are in the bag and aren't completely dislocated, Dr. Holz uses a lasso technique by passing 8-0 Gore-Tex suture threaded into the lumen of a 30-gauge needle around the haptic. If the capsule is really clean and devoid of lens cell proliferation and fibrosis, he performs an IOL exchange, removes the old lens, and places a Yamane fixated CT-Lucia lens. "If I already have to make a larger incision because I'm doing a DSAEK at the time of the exchange, then I'll use the CZ70BD lens," he explains.

For lenses that are hanging vertically

in the eye when the patient is supine because there are so many zonules missing, he first identifies the quadrant where the IOL is located. This can be demonstrated by applying pressure to the sclera around the pars plana with a muscle hook. He'll pass a 30-gauge needle through the pars plana where the lens is suspended by the few remaining zonules. "I'll lift the lens with this needle, and then use the Gore-Tex suture fixation technique in which I cannulate the TSK needle with a Gore-Tex suture, and it ends up being a lasso suture fixation," Dr. Holz says.

Dr. Holz notes that PMMA lenses that are in the sulcus and not the bag can be difficult to handle. "If I have no eyelet or fixation hole on the lens, then I remove it," he says. "Because it has to come out through a 6.5-mm wound, I'll replace this lens with a CZ70BD lens with sutured eyelets or use a Yamane fixation technique. If I have a dislocated PMMA lens that's in the capsular bag, then I'll use a Gore-Tex sutured lasso technique. If I have a PMMA lens with manipulation holes, I'll thread them with an 8-0 Gore-Tex suture using micro-grasper forceps and secure the suture to the sclera. For dislocated plate-haptic intraocular lenses, I'll generally exchange them, and I'll do a Yamane lens fixation or use the other techniques that I discussed earlier."

If a patient has a dislocated toric or multifocal IOL that's in the bag, lasso suture fixation is best, if possible, some surgeons say. Careful toric alignment and multifocal centration are critical. If the lens isn't in the capsular bag or is completely dislocated into the vitreous, then experts say these lenses must be removed. Dr. Holz recommends replacing them with monofocals.

Some patients are committed to the pursuit of re-implanting a multifocal. "I always advise against this," warns Dr. Holz. "In a few cases, I've been able to achieve a very well-centered Yamane fixation of a three-piece multifocal platform," he says. He says that this should only be attempted by surgeons who've done a large number of Yamane cases and can re-center lenses that are centering poorly intraop.

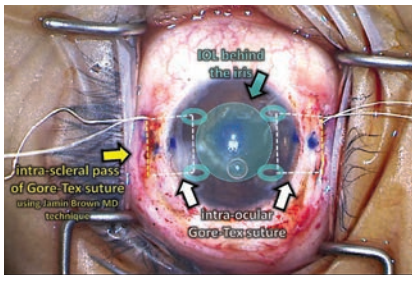


Figure 3. Gore-Tex can be used to fixate an IOL with haptic loops to the sclera. The technique shown here buries the Gore-Tex in the sclera so that the risk of erosion through the conjunctiva is virtually eliminated.

"The Achilles heel of Yamane fixation is intraocular lens decentration and tilt," he adds, noting that the patient must be counseled preop that he or she will need a second refractive surgery to fine-tune induced defocus and astigmatism, because the tilt and effective lens position are difficult to predict.

Scenarios and Techniques

Dr. Ferguson recommends preparing for many scenarios before surgery. "Have your machine ready for a pars plana vitrectomy and gather some extra supplies," he advises. "I like both the single- and double-eyelet Cionni rings. I like the Ahmed segments a lot, too. I use a double-armed Gore-Tex needle, which is a cardiovascular needle, and non-magnetized needle drivers, because if the driver is magnetized, it can be frustrating when fixating the needle; it can turn sideways or obliquely. An endoscopic cyclophotocoagulation probe is also nice to have. You can put it through a stab incision and look underneath the iris to see what you're dealing with. That was really helpful in my initial Yamane cases because I wanted to see exactly where that haptic was going through the eyewall."

For intact bags in which he's using a Cionni ring, Dr. Ferguson will put the suture through the eyelet before implanting the device. "If you preplace the suture through the eyelet, you save yourself a lot of difficulty," he says. "One warning, though: If you do that and you're using the Cionni ring, you can't put it in a shooter. However, if you use a Bechert Nucleus Rotator, you can turn the rotator's fork 90 degrees. If you just feed the Cionni ring in against that fork, it'll slide right into the bag without a shooter."

Dr. Devgan recommends taking the patient's age into consideration. "I recently saw a 25-year-old who had severe trauma," he recalls. The lens came out, he had no support, and I had to put in a lens with no easy way to secure it. I wanted to put in a lens that would last 60 years because of his life expectancy. I used Gore-Tex, which was buried within the sclera using the Jamin Brown, MD, technique, so that nothing was exposed. This will likely last for his lifetime."

It's also important to set and manage patient expectations. The original cataract surgery may produce a 20/20 result, but that shouldn't be the expectation for a second surgery, Dr. Devgan says. "I tell patients they should be happy if they get half of their vision back after a second procedure," he says. "Realistically, they can get 75 percent back, but I want to under-promise and over-deliver."

He also recommends referring the case if you're at all uncomfortable with it. "There is no harm in referring," he says. "Some of the most talented people I've seen sew in lenses are retina surgeons. In my practice, if the lens is even a little bit entwined with vitreous, I refer to a retina surgeon." REVIEW

None of the surgeons has a financial interest in any of the products or companies mentioned in this article.

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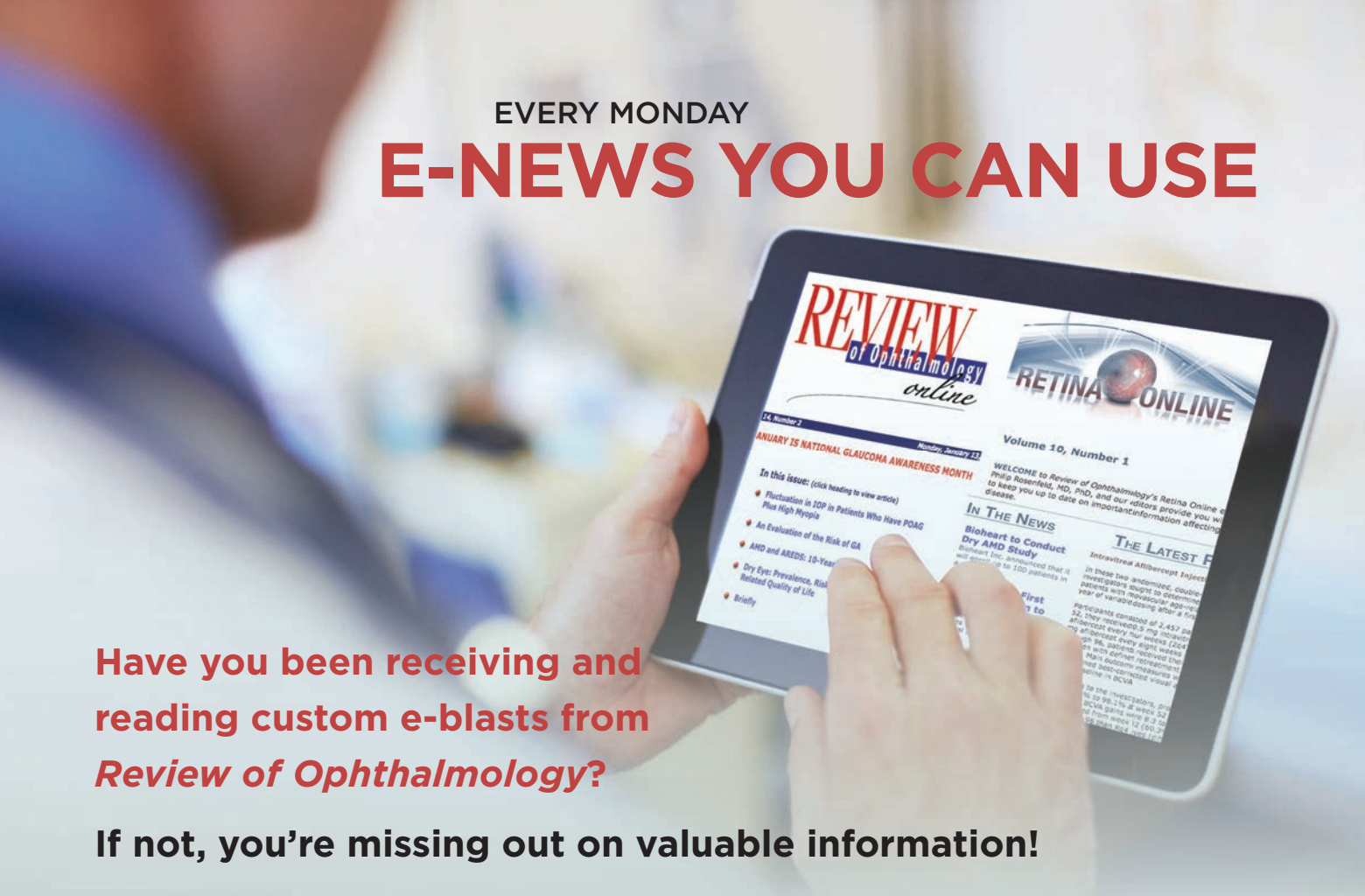

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Glaucoma and Refractive Surgery

Refractive procedures can have a profound impact on eyes at risk for glaucomatous damage. Here's how to stay out of trouble.

Sarwat Salim, MD, FACS, Boston

Refractive surgery is clearly a success story. To date, about 40 million LASIK procedures have been performed globally, and the success rate has been reported to be around 97 percent, with patient satisfaction rates around 95 percent. However, most refractive surgery patients are myopes, and myopia is a risk factor for glaucoma. This means that many patients coming in for refractive surgery are either glaucoma suspects or will develop glaucoma later in life. Couple this with the current myopia epidemic and we have a recipe for glaucoma problems both now and in the future.

In this article I'll share some tips for refractive surgeons that should reduce the likelihood of glaucoma-related problems developing in patients considering refractive surgery. Then, I'll offer some strategies glaucoma specialists can employ to manage eyes post-refractive surgery.

The Scope of the Problem

From the perspective of the refractive surgeon, the potential for many myopic individuals to develop glaucoma later in life might not seem like a big problem, since those seeking refractive surgery tend to be young and healthy. However, the reality is that we're in the midst of a myopia epidemic. In 2010 about 28 percent of the world's population was myopic, but this is projected to increase to 50 percent by the year 2050. In East Asia, myopia rates are reaching almost 90 percent.

This is concerning from a glaucoma standpoint, because many well-designed, large population-based studies have reported a two-to-four-fold increased prevalence of glaucoma among myopic subjects.[1-4] That correlation is even higher with moderate to high levels of myopia. So as more and more myopic individuals are seeking refractive surgery, it's becoming increasingly important to screen these patients with glaucoma in mind, and to be aware of the possible interactions between refractive surgery and glaucoma during and after a procedure.

The other side of this story is that an increasing number of patients requiring treatment for glaucoma have had refractive surgery in the past. This adds up to a number of special challenges for a doctor managing the patient's glaucoma. However, those challenges can be reduced if refractive surgeons take some extra steps before the procedure.

The Refractive Surgery Options

Three commonly performed refractive surgeries in the United States are LASIK, PRK and SMILE. Each can have different potential impacts on an eye at risk for glaucomatous damage, and all three can have an impact on the eye in terms of future management of glaucoma. Both refractive surgeons and glaucoma specialists need to be aware of these issues.

When LASIK is performed, a flap is created using either a microkeratome or a femtosecond laser; then the stroma is ablated to create the refractive correction. The advantage of LASIK is that the visual recovery is much faster than the recovery after PRK, but LASIK patients are prone to flap-related problems. In terms of glaucoma, one of the main issues is that when the flap is created, the

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pressure in the eye may be elevated to a very high level that can potentially further damage a compromised optic nerve.

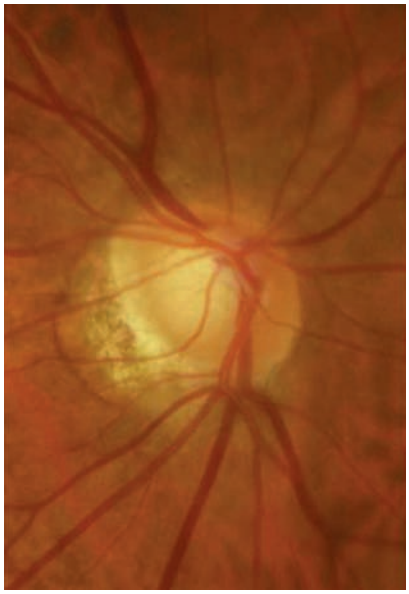
When performing PRK, the epithelium is removed mechanically or chemically; this is followed by surface ablation using an excimer laser. No flap is created, limiting complications related to increased intraoperative IOP. The downside of PRK is that removing the epithelium causes the visual recovery to take much longer than recovery from LASIK, and the recovery usually requires treatment with steroids. That's a concern for a glaucoma suspect—and even a healthy myope—because these individuals are at risk of getting steroid-induced glaucoma.

The most recent addition to the refractive surgery armamentarium is SMILE, a sort of minimally invasive version of LASIK. A femtosecond laser creates an internal lenticule of tissue in the cornea which is then removed through a small incision (about 2 mm), resulting in a refractive correction. There's no flap, and no excimer laser is involved. Because of the small incision, the visual recovery is even faster than following LASIK. Among the three procedures, SMILE may pose the least danger to myopic and/or glaucomatous eyes.

Preop Considerations

To minimize potential issues when performing refractive surgery on myopes (whether or not they qualify as glaucoma suspects or patients) and make it easier to manage glaucoma further down the line should it develop, refractive surgeons can do the following:

• ***Actively inquire about a family history of glaucoma.*** Young myopes coming for refractive surgery aren't thinking about family members who may have glaucoma. They're often young and healthy, in their 20s. Therefore, it's important for the physician to establish a good baseline with ancillary testing and to recommend close monitoring.



Myopic discs are difficult to differentiate from glaucomatous optic nerves because of vertical elongation with an oval shape, shallow diffuse cupping, temporal shift which may obscure the temporal rim, and increased incidence and extent of beta zone peripapillary atrophy.

• ***Make sure these patients understand that they have a higher-than-average risk of glaucoma in the future.*** Be sure to educate the patient about the association between myopia and glaucoma. They can't take steps to protect themselves if they don't know this is an issue.

• ***If your patient has glaucoma, consider performing SMILE or PRK instead of LASIK.*** PRK and SMILE may be better options because they don't require creating a flap, thus avoiding IOP elevation that could potentially affect an already compromised optic nerve during flap creation.

• ***Do a preop OCT glaucoma scan.*** In addition to potentially revealing information relevant to the patient's suitability for undergoing refractive surgery, this will provide a baseline for comparison if the patient develops glaucoma in the future.

• ***Do preop perimetry, especially in myopes.*** If these patients do develop glaucoma, their visual fields can be challenging to interpret because many myopic patients display visual field defects even if they don't have glaucoma. A large percentage of myopic individuals, almost 80 percent in one study, can develop visual field defects without having glaucoma. These defects often resemble glaucomatous defects—nasal steps, superior or inferior arcuate defects and paracentral defects.[5] *(See example, left.)* As a result, it's hard to distinguish which visual field abnormalities are due to myopia and which are due to new-onset glaucoma. Having a pre-refractive-surgery baseline visual field may help identify the new defects related to glaucoma.

• ***Include gonioscopy in your preop protocol, especially with hyperopes.*** Gonioscopy is routinely performed by glaucoma specialists in all patients to determine whether the angle in the eye is open or closed, and to tailor an appropriate intervention. This is typically not done by our refractive colleagues. Although I'd recommend doing gonioscopy on every pre-refractive-surgery patient, it's most important in hyperopic patients, because cases of acute angle-closure glaucoma have been reported after hyperopic LASIK.[6,7] Hyperopic patients have smaller eyes, a more congested anterior segment and narrow angles that make them susceptible to acute angle-closure glaucoma.

The other important diagnosis that can be determined by gonioscopy is pigment dispersion syndrome. At times the clinical signs of PDS may not be readily apparent on the slit lamp exam. PDS is common in myopes and is a risk factor for developing pigmentary glaucoma. Because of coexisting myopia, eyes with PDS are

PRK, LASIK and SMILE are three commonly performed refractive surgeries in the United States. Each can have different impacts on an eye at risk for glaucomatous damage. In LASIK, flap creation can elevate IOP, putting a fragile optic nerve at risk. In PRK, postop treatment with steroids can lead to steroid-induced glaucoma. SMILE may pose the least danger to glaucomatous and/or myopic eyes.

also at high risk of steroid-induced glaucoma.[8] Therefore, these patients should be closely monitored.

• ***Include disc photos in your preop protocol.*** Today, getting OCTs before refractive surgery is common. However disc photos are still very valuable, especially when it comes to myopic individuals. The optic nerve appearance in these patients can be difficult to interpret, because in a myopic eye it sometimes has an abnormal appearance that's similar to an eye with glaucoma. Having a preop baseline photo is extremely helpful for monitoring these patients over time.

I've cared for many patients with IOP measurements in the low to normal range resulting from stromal ablation after refractive surgery. In these cases, careful examination of the optic nerves and comparison to baseline optic disc photos can be extremely helpful. The stereo disc photos give us an objective way to follow these eyes. It's certainly better than going by a written description; these may differ because of inter-observer variability.

• ***Consider measuring IOP with more than one instrument.*** After refractive surgery, GAT is likely to underestimate IOP, making it difficult to both diagnose and monitor glaucoma. It's important to measure IOP with different instruments that are less likely to be affected by stromal ablation, such as the Ocular Response Analyzer or dynamic contour tonometry, for more accurate measurements.

Intraoperative IOP

Today about 70 percent of LASIK flaps are being created using a femtosecond laser, but both femtosecond laser flaps and microkeratome flaps elevate the IOP during flap creation, putting a fragile or damaged optic nerve at risk. Cases of optic neuropathy and visual field loss have been reported with the use of microkeratomes, although the underlying mechanisms remain unclear. It could be that ischemia results from the extreme elevation of IOP during the flap creation, or that it's secondary to direct trauma to the optic nerve head. IOP elevation that occurs with different femtosecond laser platforms can range anywhere from 65 to 260 mmHg, as has been demonstrated in porcine eyes. *(See table, facing page.)*

The point is that no matter how the flap is created, extreme pressure elevation can potentially occur. The elevation is transient, but reports of problems have surfaced. Maybe the problems occurred because the patients were either glaucoma suspects or had undiagnosed glaucoma. Therefore, careful screening is warranted.

Postop Considerations

Following refractive surgery, a number of glaucoma-related problems can arise:

• ***After PRK, watch for steroid-induced glaucoma.*** The biggest glaucoma-related issue in the postoperative period is associated with the use of steroids, primarily following PRK. PRK patients are often put on steroids, making them more likely to develop a steroid response.

Of course, not every patient with a higher-than-average risk for glaucoma is going to develop steroid-induced glaucoma. It depends on the dose of the medication; the chemical structure of the medication; the frequency and route of delivery, which will usually be topical in these cases; and of course the duration of the treatment. It also depends on patient-related variables such as having glaucoma, being a glaucoma suspect, having a family history of glaucoma and being myopic. Even a young, healthy patient who is a myope, or who has a family history of glaucoma is at risk of developing steroid-induced glaucoma. That means refractive surgeons need to pay attention to this.

• ***After LASIK, watch for pressure-induced stromal keratitis.*** Post-LASIK there are other concerns. One is the condition called pressure-induced stromal keratitis, or PISK. PISK causes elevated IOP and diffuse interlamellar inflammatory haze that covers most of the flap diameter. One of the issues associated with PISK is that it's easily confused with diffuse lamellar keratitis, or DLK. It's important to distinguish between them, because they're treated in opposite ways. DLK is treated with steroids, while PISK is caused by steroids. If the IOP is high because of PISK and you're just treating with

IOP-lowering medications, that's not going to help. You have to discontinue the steroids in order to achieve both resolution of the keratitis and normalization of IOP.[9-11]

There are two ways to distinguish between DLK and PISK: timing and response to treatment. DLK tends to happen soon after the refractive surgery, while PISK usually happens beyond the first postop week. The other way to tell them apart is by the response to your treatment, as mentioned above. If you mistake PISK for DLK and increase steroids, the problem will get worse.

• ***Remember that a postop loose LASIK flap or interface cyst will falsely lower the IOP measurement.*** Other postop LASIK problems that relate to glaucoma include loose flaps and interface cysts, either of which will affect the accuracy of IOP measurement when monitoring for issues such as postop steroid-induced glaucoma. When measuring IOP in the presence of a loose flap or an interface cyst, the force required to applanate the overlying flap is dampened because of the loose flap or the fluid under the cyst, causing an artificially low reading. So, you may think the pressure is normal or low when it's actually elevated. Treatment of either condition involves tapering of steroids and the use of IOP-lowering medications.[12-16]

• ***Monitor the patient regularly in the years after surgery.*** Myopia is a risk factor for glaucoma; therefore, even an uneventful surgery and postop period may eventually be followed by glaucoma. All myopic refractive surgery patients should be monitored regularly.

IOP After Refractive Surgery

As glaucoma specialists, we rely on the Goldmann applanation tonometer as our gold standard for IOP measurements. But GAT is limited in this particular population, because after refractive surgery and stromal ablation, corneal thickness varies. Goldmann designed his tonometer to be most accurate when measuring a cornea with a central corneal thickness of 520 µm. Using GAT at that thickness, the opposing forces of surface tension and corneal rigidity balance each other out and can be ignored. But after a cornea has undergone refractive surgery, that magic number is no longer useful. As a result, most studies in the literature indicate that GAT underestimates IOP after refractive surgery.

That's very important, because if pressure is being measured low, we can mistakenly believe a patient is normal when he isn't. It's critical in such cases to look at other parameters during our examination and testing to make sure we're not missing glaucoma in these individuals—and we have to choose our method of IOP measurement carefully.

Important things to keep in mind include:

• ***Be aware that glaucoma patients may not mention past refractive surgery.*** Patients who had refractive surgery 20 years ago sometimes think it was just some minor procedure that no longer matters. They won't volunteer the information unless you actively seek it. I've learned to ask patients specifically if they were very nearsighted early in life and whether they've had LASIK or PRK.

• ***Obtain any pre-refractive-surgery data that you can.*** Although we don't have any algorithms for converting baseline IOP data to current equivalents, it's helpful to know how high the patient's myopia was and/or how much ablation was done. This information can help approximate the real IOP.

• ***The change in IOP correlates with the ablation depth.*** The more ablation was done, the more the CCT is reduced and the greater the impact on measured IOP.

• ***The decrease in measured IOP is more pronounced in myopic patients than hyperopic patients, for both LASIK and PRK.*** Although I don't know for certain why this is true, it could have something to do with the elongated shape of the myopic eye, which can be associated with a thinner cornea. Another possible explanation is that a myopic ablation is usually focused on the center of vision—where GAT is typically measured—while hyperopic ablation tends to focus pericentrally.

• ***It's important to measure IOP with more than one instrument.*** Since GAT is likely to underestimate IOP, we should be measuring IOP using different instruments. The more information you have, the better. Currently, several tonometers are available to us, including the tonopen, pneumotonometer, ORA and DCT.

Some of these can be used to measure IOP at the periphery of the cornea after refractive surgery, instead of in the center. However,

IOP During Femtosecond Flap Creation (mmHg)

	Intralase	Femtosecond LDV	VisuMax	Femtec
Mean maximum IOP, regular procedure	135 ±16	184 ±28	65 ±20	205±53
Mean maximum IOP, worst case procedure	260 ±53	No data	105 ±13	248±51

IOP can spike during femtosecond flap creation because of the suction on the eye. In a study conducted in 2011, four different lasers used on cannulated porcine globes produced very different IOP spikes. The "worst case" measurements in the table were created by pressing the interface against the globe until the applanation was automatically aborted.[29]

it's important to keep in mind that the peripheral cornea tends to be thinner than the central cornea, even if the refractive surgery hasn't altered the periphery. That means that peripheral IOP measurements will always tend to be a little lower than central measurements. Again, this kind of strategy is most helpful if such a measurement was taken prior to the refractive surgery, allowing a fair comparison.

Two tonometers that seem to be better at measuring post-refractive-surgery IOP are the ORA and the DCT. Their measurements have been shown to be less affected by stromal ablation.[17-21] For example, the DCT consists of an electronic strain gauge that's embedded in a contoured plastic tip. When the DCT measures IOP, it doesn't applanate the corneal tissue, making the measurement independent of corneal properties. The ORA measures corneal hysteresis, a measure of the resiliency or shock-absorbency of the cornea, in addition to IOP, using a rapid air impulse to apply force to the cornea. It then adjusts the IOP measurement to take the corneal hysteresis into account. Studies suggest that this results in an accurate IOP measurement despite corneal alterations from refractive surgery. *(For more on the ORA, see the Point/Counterpoint on p. 64.)*

• ***Remember that structural imaging (including OCT) seems to be unaffected by refractive surgery.*** Most studies have demonstrated that there are no changes in retinal nerve fiber layer thickness measurement after refractive surgery.[22-26] These findings have been confirmed in microkeratome-assisted LASIK, femtosecond assisted LASIK and SMILE. This means we don't have to develop a new baseline for imaging in these patients. That's good, because imaging has become a routine part of glaucoma evaluation and often provides evidence of structural damage before functional loss occurs.

However, it's also important to remember that most refractive surgery patients are myopes, and myopes tend to have artifacts on OCT simply because of their eye structure. A comparison to a baseline scan can still be revealing, though, since changes can be observed, even in the presence of artifacts.

Most studies have demonstrated that there are no changes in retinal nerve fiber thickness measurement after refractive surgery, so we don't have to develop a new baseline for imaging.

• ***Be aware that visual field changes can result from issues with the way the refractive surgery was performed.*** At least one study conducted back in 2005 reported that visual field changes occurred after LASIK in the absence of optic nerve or retinal nerve fiber layer damage.[27,28] The authors concluded that this was due to under-ablation of the paracentral cornea, causing irregular optical zones. Obviously, the nature of LASIK surgery and the algorithms used today are far better than those in use 15 years ago, but the possibility that the refractive surgery may be affecting the visual field is worth keeping in mind, since some of your glaucoma patients may have had refractive surgery that long ago.

Making the Best of It

There's no question that refractive surgery and glaucoma each affect the other. Myopia is a risk factor for glaucoma and a major driver of individuals seeking refractive surgery; therefore, overlap is inevitable. Given this reality, both refractive surgeons and glaucoma specialists can help patients by acknowledging this overlap and taking steps to mitigate any damage.

Refractive surgeons can help these patients by doing three things:

1) Assist the doctors who may treat glaucoma in these patients later on by doing a few extra things before surgery: proactively inquire about any family history of glaucoma; educate myopic patients about their increased risk of glaucoma and advise them to have regular follow-ups; perform a comprehensive exam, including gonioscopy and IOP measurements using different devices; and obtain baseline ancillary tests, including disc photos, imaging and visual fields.

2) Do what you can to avoid worsening any existing problem during the surgery, by avoiding flap creation if possible, or using a flap creation system that doesn't raise IOP too excessively, to minimize damage to an already compromised nerve.

3) Be alert for the presence of steroid-induced glaucoma, pressure-induced stromal keratitis, an interface cyst or a loose flap during the postop period.

Glaucoma specialists can help these patients by:

1) proactively inquiring about refractive surgery in the past;

2) obtaining any pre-refractive-surgery data that may be available;

3) measuring IOP in ways that are the least likely to be altered by the earlier refractive surgery; and

4) paying attention to other parameters of glaucoma evaluation in the presence of inaccurate IOP measurements. REVIEW

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mology, vice chair of clinical and academic affairs, and director of the Glaucoma Service at Tufts University School of Medicine. She is a consultant and speaker for Aerie Pharmaceuticals and a speaker for Bausch + Lomb.

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Phase III Trials in Wet AMD–What's Next?

A look at the drugs and devices closest to the clinical-trial finish line in the United States.

Rebecca Russ Soares, MD, MPH, Raziyeh Mahmoudzadeh, MD, and Michael N. Cohen, MD

Though intravitreal anti-vascular endothelial growth factor agents are the mainstay of treatment for neovascular age-related macular degeneration, frequent and repeated injections are required in order to maintain the visual gains the drugs provide.[1] This represents a substantial treatment burden to patients, with significant associated time and financial costs.[2] Unfortunately, the need for frequent injections can often pose problems to treatment adherence and cause patients to be lost to follow-up.[3] As a result, in recent years there's been an increased focus on improving durability in novel therapeutics for nAMD in order to reduce this burden. In this article, we'll review the current status of several nAMD medications that are now undergoing, or have recently completed, their Phase III clinical trials *(Figure 1)*.[4]

Brolucizumab (Novartis)

Though brolucizumab was approved by the Food and Drug Administration in October 2019 and is already on the market,[5] it's still undergoing Phase III and IV clinical trials to explore its safety and efficacy. Brolucizumab is an anti-VEGF-A antibody grafted to a human single-chain antibody fragment. Use of the single chain fragment, the smallest antibody unit, allows for a greater dose of anti-VEGF per unit of volume.[6,7] This allows higher concentration in the vitreous and more penetrability of the retina and RPE. Furthermore, a higher dose per unit of anti-VEGF can allow for slower clearance from the eye, and multiple studies have shown that brolucizumab can potentially allow for extended dosing schedules. In the first Phase I/II human trial of brolucizumab, the median time for re-dosing anti-VEGF after receiving brolucizumab 6 mg was 30 days longer than the median time required for re-dosing anti-VEGF after receiving ranibizumab.[8] The Phase II study OSPREY, which found non-inferiority of brolucizumab 6 mg to aflibercept 2 mg dosed at eight weeks, laid the foundation for 12-week dosing.[7]

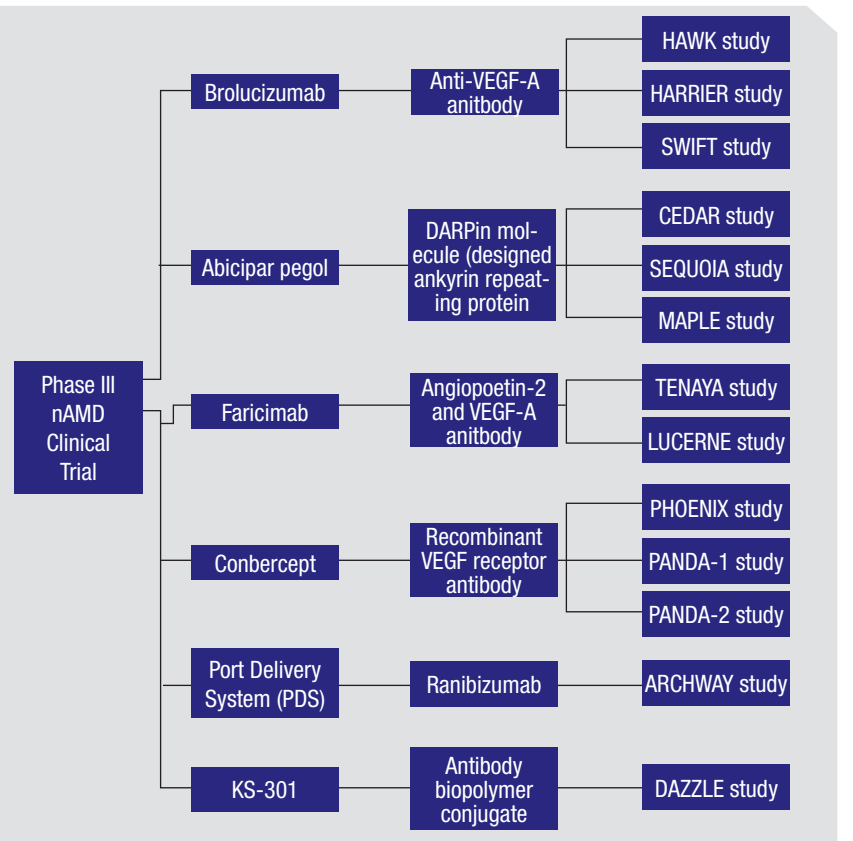
The Phase III trials that paved the way for FDA approval of brolucizumab were HAWK and HARRIER. HAWK randomized 1,082 patients to three groups in a 1:1:1 fashion: brolucizumab 3 mg or 6 mg or aflibercept 2 mg. HARRIER randomized 743 patients equally to either brolucizumab 6 mg or aflibercept 2 mg. In both trials, all groups received a loading dose of three monthly treatments. Additionally, aflibercept was dosed every eight weeks, whereas brolucizumab was initially dosed every 12 weeks. If disease activity was detected by pre-specified functional and structural measures, those in the brolucizumab group permanently dropped down to eight-week dosing. At Week 48, the primary endpoint of each trial was achieved, with brolucizumab demonstrating noninferiority to aflibercept in BCVA change from baseline. In each group there was an improvement in visual acuity by about six to seven ETDRS letters over 48 weeks. Also, 56 percent of patients in HAWK and 51 percent of patients in HARRIER were able to stay on 12-week dosing of brolucizumab. Patients on brolucizumab also had a greater significant reduction in central subfield thickness as compared to those on aflibercept.[6]

Although the overall safety profiles between brolucizumab and aflibercept were initially thought to be simi-

lar,[6] brolucizumab has since come under scrutiny for reports of vision loss secondary to severe noninfectious uveitis and occlusive retinal vasculitis.[9] The American Society of Retina Specialists and Novartis have been diligent about continued surveillance, and Novartis has launched a new website that provides updates of significant adverse events. As of June 2020, the incidence of retinal vasculitis and/or occlusion is 8.65 per 10,000 injections. Novartis and the ASRS have not recommended against use of the medication but encourage physician vigilance in looking for signs of inflammation.[10,11]

Several other Phase IIIb trials are under way and remain active. One recent addition is the SWIFT study, a new single-arm trial that will evaluate patients to determine the effect of brolucizumab using a treat-and-extend regimen in patients with nAMD. Patients receive three monthly doses of brolucizumab, and then are extended by four weeks up to a 16-week interval. The primary outcome is the proportion of patients with no disease activity at week 48.[12]

nAMD Treatments in Phase III Clinical Trials



Abicipar pegol (AbbVie/ Allergan & Molecular Partners)

Abicipar pegol is a designed ankyrin repeating protein (DARPin) molecule. It's a recombinant protein that binds all isoforms of VEGF-A. Its small size allows for easily achievable higher molar concentration, leading to higher vitreous concentration and better tissue penetration. Furthermore, since its molecules have high binding affinity and good stability it has the potential to be quite durable.[13]

In October 2019, Allergan and Molecular Partners announced their two-year data from two identical Phase IIIa trials, CEDAR and SEQUOIA, evaluating the efficacy and safety of abicipar as compared to ranibizumab. Patients with nAMD were assigned to receive abicipar 2 mg every eight weeks after a loading dose of three monthly injections; abicipar 2 mg every 12 weeks after a loading dose of two monthly injections followed by an injection after eight weeks; or ranibizumab 0.5 mg monthly.[14,15] The primary outcome for each of the studies was the proportion of patients with stable vision, defined as a change in vision by no more than 15 ETDRS letters.

At 52 weeks, abicipar met the noninferiority criteria for the primary outcome in both the q8 and q12 week dosing arm, with 93 percent and 90 percent of patients maintaining baseline vision in pooled results from both studies. Secondary endpoints, such as mean best-corrected visual acuity, were maintained from year one to year two across all arms, and central subfield thickness decreased at year one and again at year two across all arms.[16]

In year one there were initial concerns about high rates of new-onset intraocular inflammation: 15.4 percent in the abicipar every-eight-week group and 15.1 percent in the abicipar every-12-week group, as compared to none in the ranibizumab group.[17] New intraocular inflammation declined in the second year of the study, with a pooled rate of 1.9 percent in both abicipar arms and 1 percent in the ranibizumab arm.[16] Because of these initial safety concerns, the MAPLE study, a 28-week safety evaluation, was performed to determine the rates of adverse events in 128 patients after the manufacturing process was changed. The study

had a single arm of nAMD patients treated with a loading dose of three monthly injections followed by injections every eight weeks. The study found a lower rate, 8.9 percent, of intraocular inflammation than CEDAR and SEQUOIA. The incidence of severe intraocular inflammation was 1.6 percent.[17]

In late June of 2020, the FDA didn't approve abicipar pegol for use, citing that the rates of observed intraocular inflammation resulted in an unfavorable benefit-risk ratio in the treatment of patients with neovascular AMD. AbbVie, which has completed its acquisition of Allergan, has yet to formally announce any plans regarding the future of the molecule.[18]

Faricimab (Roche/Genentech)

Faricimab is a novel antibody that's bi-specific, inhibiting both angiopoetin-2 and VEGF-A. This bi-specificity is theorized to lead to sustained efficacy. The 52-week results of the Phase II STAIRWAY study were previewed at the 2018 American Academy of Ophthalmology's meeting and the 2020 virtual meeting of the Association for Research in Vision and Ophthalmology. The study had three arms, evaluating 76 patients with nAMD who were randomized to either faricimab 6 mg every 12 or 16 weeks (after initial monthly loading doses) or ranibizumab 0.5 mg every four weeks.[19,20] At week 24, 65 percent of patients treated with faricimab had no active disease. People dosed every 16 weeks had a mean best-corrected visual acuity improvement of 11.4 mean letters from baseline at week 52. At 52 weeks, faricimab every 12 weeks provided a gain of 10.1 letters vs. 9.6 letters with ranibizumab.[19, 21] Each arm of the trial had a similar proportion of greater than 15 letters gained and fewer than 15 letters lost. There were no appreciable differences in adverse events or other safety outcomes.[21] Following the success of the Phase II trial, two identical, multicenter Phase III trials, TENAYA and LUCERNE, are under way to further evaluate safety and efficacy. The studies have enrolled 1,280 participants, randomized to faricimab every 16 weeks—with the possibility of decreasing the interval to every 12 or eight weeks—or aflibercept every eight weeks.[22] The primary outcome measure is the average change of BCVA from baseline to week 48 in the patients. The targeted completion date is the fall of 2022.[23,24]

Faricimab's bi-specificity—it inhibits both ANG-2 and VEGF-A—may lead to a sustained effect.

Conbercept (Chengdu Kanghong Biotech)

Conbercept is a recombinant VEGF receptor antibody, thought to have improved stability over aflibercept because of its combination of the second immunoglobulin domain of VEGFR1 and the third and fourth immunoglobulin domain of VEGFR2.[25] The PHOENIX trial was a 12-month, randomized, Phase III trial of conbercept performed at nine locations throughout China that enrolled 114 patients. The study evaluated intravitreal injections of conbercept 0.5 mg with a three-month loading dose followed by quarterly injections. The control group received a delayed regimen: sham injections (as there were no previously approved anti-VEGF agents in China) monthly for three months, followed by three monthly injections, followed by quarterly injections up until 12 months. The primary outcome was mean change in BCVA at three months.

At this three month primary endpoint, there was a statistically significant difference in the change in BCVA from baseline, with a gain of 9.2 letters in the conbercept group and a gain of only 2.02 letters in the sham group. At one year, and after both groups received the study medication, there was improved BCVA from baseline, with the conbercept group showing an increase in BCVA by 9.98 letters and the (initial) sham group showing a gain of 8.81. This difference wasn't statistically significant at the 12-month endpoint. Though there were no significant safety concerns during the study, PHOENIX wasn't adequately powered to detect all adverse events.[26]

After the National Medical Products Administration's (the Chinese equivalent to the U.S. Food and Drug Administration) approval of conbercept in 2013, the U.S. FDA expedited conbercept to undergo Phase III clinical testing without repeat Phase I or II trials in the United States. Beginning in 2018, two parallel Phase III studies, PANDA-1 and PANDA-2, were tasked to evaluate conbercept globally in treatment-naïve nAMD patients. Both trials will evaluate the safety and efficacy of conbercept 0.5 mg at eight-week intervals and conbercept 1 mg at 12-week intervals, as compared to aflibercept 2 mg at eight-week intervals (control arm), after each arm receives three monthly loading doses. The combined enrollment target is 1,140 patients, randomized evenly between the three arms. The primary endpoint is the change in BCVA at 36 weeks from baseline. Secondary outcomes include evaluating both

functional and structural improvements. The main difference between PANDA-1 and PANDA-2 is that the former follows continuous dosing at the above intervals through week 92. At week 40, PANDA-2 adopts *pro re nata* injections up to a cap of 16-week intervals. Each study is expected to finish by 2022.[27,28]

Port Delivery System (Roche/Genentech)

While other Phase III trials discussed thus far have focused on novel therapeutics, the port delivery system, or PDS, focuses on a novel delivery system. The PDS is an implant designed to administer a highly concentrated form of ranibizumab over an extended period. After the device is surgically implanted through an incision in the sclera at the pars plana *(Figure 2)*, it continuously releases ranibizumab into the vitreous via passive diffusion. The self-sealing device can then be refilled in the office via injection through the conjunctiva.

The Phase II randomized controlled clinical trial, LADDER, demonstrated initial visual and anatomic success with the PDS. The trial randomized 220 nAMD patients in a 3:3:3:2 ratio to four different arms: ranibizumab 10 mg/ml, ranibizumab 40 mg/ml, or ranibizumab 100 mg/ml using the PDS or standard monthly intravitreal ranibizumab 0.5-mg injections. The PDS with 100 mg/ml of ranibizumab demonstrated the longest median time until refill, at 15 months, compared to 8.7 and 13 months in the 10 mg/ml and 40 mg/ml groups.

In terms of visual outcomes, at nine months, the BCVA change from baseline was a loss of ETDRS letters in the PDS 10 mg/ml and 40 mg/ml. By comparison, there was a gain of 5.1 and 3.9 ETDRS letters in the PDS 100 mg/ml and monthly intravitreal ranibizumab 0.5 mg arms, respectively. Mean CFT change from baseline was similar at nine months between the 100 mg/ml PDS and monthly ranibizumab groups. The primary adverse event was vitreous hemorrhage, which occurred at a rate of 4.5 percent.[29]

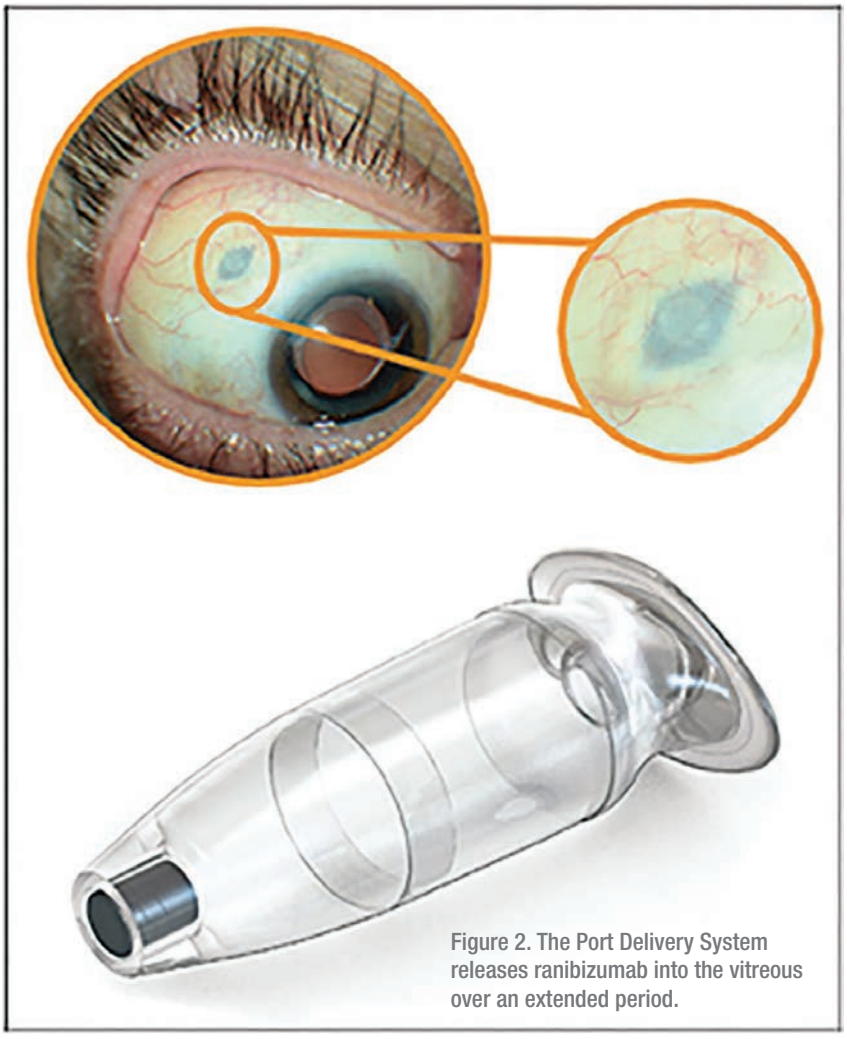


Figure 2. The Port Delivery System releases ranibizumab into the vitreous over an extended period.

Given the success of the Phase II trial, the PDS is undergoing an additional Phase III study, ARCHWAY, which began in 2018 and is estimated to finish in 2022. The study randomized patients to PDS 100 mg/ml at baseline with fixed refill intervals of 24 weeks. The control arm is monthly intravitreal injections of 0.5-mg ranibizumab. The primary endpoint, the change in BCVA, will be determined by averaging the BCVA scores of weeks 36 and 40 and comparing that value to the baseline score. Secondary outcomes include evaluating the change in central subfoveal thickness from baseline, and rates of adverse events.[30]

In addition, PORTAL is an extension Phase III study designed to look at long-term safety, both ocular and systemic, of the PDS 100 mg/ml in patients who have completed the ARCHWAY or LADDER trial. Those who received monthly intravitreal injections were also eligible for PDS implantation. The study plans to evaluate patients with the

PDS receiving in-office refills every 24 weeks for 144 weeks.[31]

KSI-301 (Kodiak Sciences)

KSI-301 is an anti-VEGF IgG1 antibody linked to a high molecular weight biopolymer. The large molecule allows for high molar concentrations of anti-VEGF-A binding capability, which is posited to extend durability. In Phase Ib, 35 patients with treatment-naïve nAMD were given 2.5- or 5-mg doses of KSI-301. At 16 weeks, best-corrected visual acuity improved by a mean of 5.4 letters, and after three monthly loading doses, 80 percent were able to extend their treatment intervals to as long as four months before the next injection.[32] Its success in Phase Ib has led to a pivotal Phase IIb/III trial called DAZZLE. Estimating an enrollment of 550 participants, DAZZLE will randomize patients to receive KSI-301 5 mg or sham at 12-, 16- and 20-week intervals. A comparator arm will enroll participants to receive aflibercept 2 mg or sham for three monthly loading doses followed by every-eight-week injections. Primary outcome is the mean change in best-corrected visual acuity at a year.[33]

In conclusion, with a focus on enhanced duration, the current Phase III clinical trials in nAMD provide new hope for expanding our therapeutic armamentarium. Taken together, these new therapies could provide a more comprehensive approach to caring for patients with nAMD. REVIEW

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Dr. Cohen is a consultant for Allergan.

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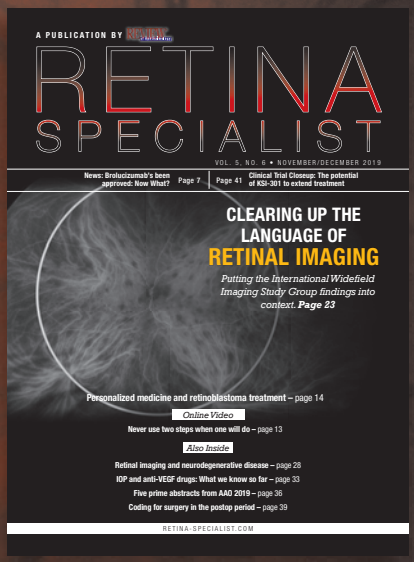

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The Eye is the Window to the Heart

Researchers in South Korea say that physicians may be able to better predict a patient's risk of a cardiovascular event by using a deep-learning program to evaluate the patient's fundus.

In the retrospective cohort study, the surgeons trained a deep-learning model using 15,408 images from the Health Promotion Center of the Seoul National University Hospital. They trained the program to predict carotid artery atherosclerosis from the images, and called the result the deep-learning fundoscopic atherosclerosis score (DL-FAS). They then constructed a retrospective cohort of patients between 30 and 80 years of age who had completed elective health exams at the hospital.

For predicting carotid artery atherosclerosis among subjects, the model achieved an area under receiver operating curve of 0.713, and area under the precision-recall curve of 0.569. The accuracy was 0.583, the sensitivity was 0.891 and the specificity was 0.404. The positive and negative predictive values were 0.465 and 0.865, respectively.

In the cohort, which consisted of 32,227 participants, there were 78 cardiovascular disease (CVD) deaths, and follow-up visits every 7.6-years (median). Those with DL-FAS greater than 0.66 had an increased risk of CVD deaths compared to those with DL-FAS <0.33 (hazard ratio: 8.33; 95% confidence interval [CI], 3.16-24.7). Risk association was significant among intermediate and high Framingham risk score subgroups. The researchers found that the DL-FAS improved the concordance by 0.0266 (95% CI, 0.0043-0.0489) over the FRS-only model.

Ultimately, the physicians say that the deep-learning program's DL-FAS score was an independent predictor of CVD deaths when adjusted for FRS and even had an added predictive value beyond the FRS.

Amer J Ophthalmol 2020;217:121-130.
Chang J, Ko A, Park SM, et al.

Accuracy of Next-gen IOL Formulas in Vitrectomized Eyes

Physicians from Guangdong, China, analyzed the latest intraocular lens formulas' performance in eyes that had undergone vitrectomies.

The study was a retrospective, consecutive-case-series review of 111 eyes of 111 patients that underwent uneventful phacoemulsification and IOL implantation after vitrectomy. The surgeons divided the patients into four groups according to whether the posterior chamber was filled with silicone oil. They then evaluated the performance of several IOL formulas, with and without lens-constant optimization.

The researchers say that, before lens-constant optimization, the mean prediction errors (MEs) of all formulas were statistically different from zero (0.14 to 0.46 D) in vitrectomized eyes, except for the Kane formula. The Barrett Universal II, Emmetropia Verifying Optical, Kane and Haigis formulas all had relatively lower mean absolute error (MAE) and median absolute error (MedAE) with optimized constants. The doctors found no significant systemic bias in the new formulas for vitrectomized eyes with axial lengths greater than 26 mm ($p>0.05$).

The Hoffer Q and Holladay 1 displayed significant hyperopic shift (0.39 and 0.51 D) for long eyes, which was corrected by the Wang-Koch axial length adjustment. The researchers report that there were no significant differences in the prediction accuracy of all formulas among the four subgroups ($p>0.05$).

The physicians say that the BUII, EVO, Kane and Haigis displayed comparable performance in vitrectomized eyes with optimized constants. In vitrectomized highly myopic eyes, the new formulas and traditional formulas with WK adjustment exhibited "satisfactory prediction accuracy." Silicone oil tamponade didn't affect the prediction accuracy of formulas when using the IOLMaster 700. REVIEW

Amer J Ophthalmol 2020;217:81-90.
Tan X, Zhang J, Zhu Y, et al.

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

—Keith H, retinal prosthesis recipient

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A New Option for Allergy Sufferers

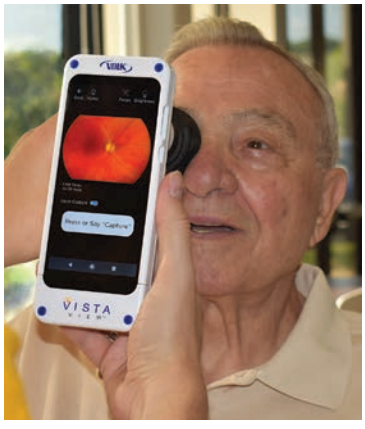
Bausch Health Companies, Bausch + Lomb and Eton Pharmaceuticals announced that the FDA has approved Alaway Preservative Free (ketotifen fumarate ophthalmic solution 0.035%), antihistamine eye drops (EM-100), as the first over-the-counter, preservative-free formulation eye drop approved to temporarily relieve itchy eyes due to pollen, ragweed, grass, animal hair and dander. The company says it avoided using preservatives in the formulation because common preservatives can cause allergic reactions in some people that may lead to ocular redness, irritation, itching or tearing. B+L says Alaway Preservative Free is formulated to relieve itch within minutes and can provide up to 12 hours of eye itch relief with one dose. For information, visit bausch.com.

Fundus Imaging Anywhere

If you regularly visit patients in nursing homes, need to get a fundus image in the parking lot to follow your COVID-19 protocols or participate in screening events, Volk Optical says its new VistaView portable mydriatic retinal camera may be worth a look.

The VistaView integrates Volk's high-resolution, all-glass, double-aspheric optics with an intuitive digital platform to capture sharp, wide-field fundus images while managing patient data right on the device, the company says.

Volk says the VistaView is an all-in-one device that offers the widest field of view of any mydriatic fundus camera in its class at 55 degrees. The onboard application includes features such as image review, enhancement and analysis; and instant password-protected report generation and transmission.



A voice-capture option leaves both hands free to position the device for the best quality images, the company adds. The device has both autofocus and manual focus modes, as well as an illumination adjustment to help make photophobic patients more comfortable. Password protected reports and DICOM images are easily shared or exported for billing, consultation and referral, Volk says.

For information, visit volk.com/vista.

Glide into Easier Glaucoma Surgery

If you routinely perform the Kahook Dual Blade glaucoma procedure, or are considering adding it to your arsenal, New World Medical recently announced a new instrument that might make it easier for you.

The company says that the new KDB Glide is designed to give surgeons a refined, precise experience performing excisional goniotomy. New World Medical says the new device improves on the successful Kahook Dual Blade technology by adding new features: A rounded heel, tapered sides and a smaller footplate deliver optimal interface with the canal of Schlemm, permitting a precise excision with the instrument's dual blades, even in variable anatomy.

If you're new to excisional goniotomy procedures for the treatment of glaucoma, they involve removing a segment of the diseased trabecular meshwork, which surgeons say facilitates the flow of aqueous into collector channels of the eye, thus alleviating intraocular pressure. For information, visit newworldmedical.com. REVIEW

This article has no commercial sponsorship.

A conjunctival mass brings a 20-year-old woman to Wills Eye Hospital for a consultation.

Charles Brodowski, MD, Tatyana Milman, MD, and Christopher Rapuano, MD

Presentation

A 20-year-old Caucasian female was referred for evaluation of an enlarging left conjunctival lesion. One month prior to presentation the patient had noticed what she perceived to be a "popped blood vessel" in the conjunctiva of her left eye. She noted mild redness around the lesion, but denied pain or discharge. Vision was stable with glasses. There was no history of ocular trauma or contact lens wear. The review of systems was within normal limits. The lesion didn't respond to topical tobramycin initiated by the referring ophthalmologist.

Medical History

The patient had no significant past medical or surgical history. Family history was positive for a thyroid disorder in her mother. The patient was a non-smoker, and denied illicit drug use. She reported having an allergy to doxycycline.

The patient's medication list included pantoprazole 20 mg tablet two times per day and a combination oral contraceptive daily.

Examination

Best-corrected visual acuity was 20/25 in the right eye and 20/30+1 in the left. Pupils were equal, round and reactive bilaterally with no relative afferent pupillary defect. Intraocular pressure was 20 mmHg in both eyes. Visual fields were full to confrontation bilaterally. Extraocular motility was full bilaterally. There was no evidence of proptosis. Adnexa and eyelid examination was within normal limits bilaterally.

Slit lamp examination of the left eye demonstrated a circumscribed, soft, solid, yellow-orange, dome-shaped, temporal juxtalimbal subepithelial epibulbar nodule that measured 3 x 3 mm *(Figure 1)*. A prominent vessel was noted temporal to the lesion. There were no associated cysts or pigmentation. The lesion was slightly mobile and did not appear to be completely adherent to the underlying sclera. The remainder of the anterior segment and funduscopic examination in both eyes was unremarkable.

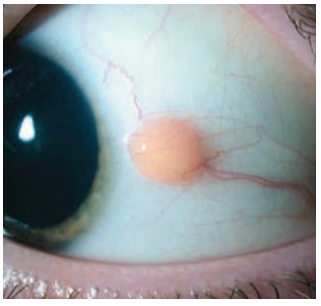


Figure 1. External photograph demonstrating a yellow-orange, dome-shaped, juxtalimbal subepithelial mass.

Based on this information, what's your diagnosis? The diagnosis appears below.

Workup, Diagnosis and Treatment

Figure 2. Optical coherence tomography of the conjunctival lesion demonstrating a hypoechoic, solid lesion without evidence of invasion to surrounding tissues.

The differential diagnosis of progressive, dome-shaped, yellow-orange subepithelial epibulbar nodule in a young patient includes reactive and inflammatory lesions, such as pyogenic granuloma, juvenile xanthogranuloma, nodular fasciitis and keloid. Benign neoplasms, such as dermolipoma/lipoma, amelanotic conjunctival nevus, fibrous histiocytoma, myxoma and conjunctival stromal tumor/ fibroma are also diagnostic considerations. Amyloid deposits and lymphoproliferative lesions, including benign reactive lymphoid hyperplasia and pediatric follicular lymphoma, may present similarly. Other malignant neoplasms, such as melanoma and various sarcomas are much less likely given the patient's

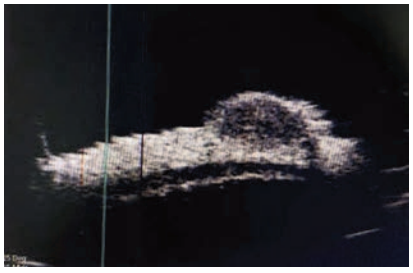


Figure 3. Ultrasound biomicroscopy of conjunctival lesion demonstrating a primarily superficial lesion without invasion of sclera, iris, ciliary body, or anterior chamber angle.

age and the overall benign appearance of the lesion.

Corneal topography was subsequently obtained, which documented regular astigmatism; no other corneal pathology was noted. Optical coherence tomography demonstrated a well-circumscribed hypoechoic, solid lesion *(Figure 2)*. Ultrasound biomicroscopy showed a hypoechoic, primarily superficial lesion without significant invasion of the sclera, anterior chamber angle, ciliary body or iris *(Figure 3)*.

Following imaging modalities, treatment options were discussed, including observation, topical corticosteroids and excisional biopsy. Ultimately, because neoplastic diseases were considered, the excisional biopsy with double freeze-thaw cryotherapy and conjunctivoplasty were performed. On the operative day, which was approximately six weeks after the patient's initial presentation, the lesion was noted to have significant growth *(Figure 4)*.

Figure 4. Preoperative photo demonstrating significant growth of the conjunctival lesion.

Histopathologic analysis of the lesion demonstrated a stromal infiltrate of macrophages, including xanthoma cells and Touton-type giant cells, lymphocytes and rare eosinophils in a background of small vascular channels *(Figures 5 and 6)*. Immunohistochemical stains showed that macrophages stained positive for a macrophage marker CD163

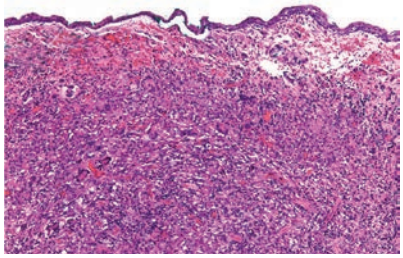


Figure 5. Microscopic findings. Mixed inflammatory infiltrate in the conjunctival substantia propria in a background of small vascular channels.

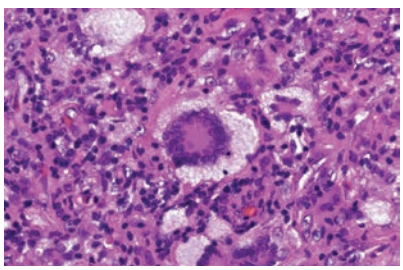


Figure 6. Microscopic findings. Higher magnification demonstrates multinucleated Touton-type giant cells, with a wreath-like nuclear arrangement, homogeneous central eosinophilic cytoplasm, and a peripheral pale-pink frothy lipidized rim. Numerous small lymphocytes are present in the background.

and negative for Langerhans' cell markers S100 and C1a. Although the macrophages were negative for mutant BRAF V600E, there was a strong and diffuse nuclear positivity for Cyclin D1, suggestive of mitogen-activated protein kinase (MAPK) signaling pathway activation. The combined clinical, morphologic, and immunohistochemical findings were compatible with an epibulbar (corneoscleral limbal) juvenile xanthogranuloma (JXG).

The patient experienced no immediate postop complications. She was seen postoperative day one, presenting with a subconjunctival hemorrhage of the left eye. At the surgical site the limbal sutures were intact with well-apposed conjunctiva. Vision was stable. On postoperative day one she was started on a topical neo-poly-dex four-week taper. She was seen postoperative week one and showed a resolving subconjunctival hemorrhage. Sutures remained in place, and no evidence of tumor recurrence was evident. Vision remained stable. The patient was advised to continue her topical neo-poly-dex taper, and to follow-up in six weeks for further evaluation.

Discussion

JXG is defined as a collection of histiocytes within a granulomatous reaction that doesn't meet criteria for the diagnosis of Langerhans' cell histiocytosis (LCH). JXG is the most common of non-LCH histiocytoses, classically presenting as single or multiple red-yellow-brown papules and/or nodules of the face, neck and trunk.[1,2] Although up to three-quarters of JXG lesions arise within the first year of life, JXG can also present in older patients.[2]

While the majority of JXG lesions involve the skin, the disorder can involve extracutaneous sites, with the eye the most frequently affected.[3] In a retrospective interventional case series of 30 patients with ocular JXG, the iris was the most common site (n=21, 68 percent), with the conjunctiva (n=6, 19 percent), eyelid (n=2, 6 percent), choroid

(n=2, 6 percent), and orbit (n=1, 3 percent) less commonly affected.[4] Presenting symptoms of ocular JXG include spontaneous hyphema (most common), increased IOP, blurry vision, heterochromia, eye redness and conjunctival mass.[4] An adult variant of JXG which shares many clinical and histologic similarities, called adult-onset xanthogranuloma (AOX), typically presents as an orbital mass or a nodule at the corneoscleral limbus, which progressively increases in size.[5] Pediatric JXG can be disseminated and can be associated with other systemic diseases, including neurofibromatosis 1 (NF1), Niemann-Pick disease, urticaria pigmentosa and juvenile myelomonocytic leukemia (JMML).[5,6] AOX is an isolated lesion, and is confined to a singular ocular region.[7] It's important to note that periocular xanthogranulomatous orbital disease in adults can occur in a setting of adult-onset asthma, necrobiotic xanthogranuloma (associated with hematolymphoid malignancies) and Erdheim-Chester disease (a systemic histiocytic/dendritic cell neoplasm with frequent BRAF V600E mutations). Thus, the diagnosis of isolated AOX should be made only after careful exclusion of xanthogranulomatous diseases that have systemic implications.

JXG and AOX are diagnosed clinically with histopathologic confirmation. Clinical exam classically shows a well circumscribed, nodular or dome-shaped yellow-to-orange lesion. Histopathologic analysis of both entities classically shows a collection of foamy histiocytes, lymphocytes, fibroblasts, eosinophils and Touton-type giant cells. The presence of Touton-type giant cells is a characteristic finding in various xanthogranulomatous diseases, including JXG/AOX.[8,9] Immunohistochemically, JXG and AOX macrophages demonstrate positivity for CD68 and CD163, and are negative for Langerhans' cell markers for S100, CD1a, and Langerin, which distinguishes JXG/AOX from LCH.[10]

Many theories have been proposed regarding the pathogenesis of JXG/AOX, however at this time the exact cause is not clearly understood. One hypothesis suggests that localized JXG/AOX may originate from a histioxanthomatous reaction response to local tissue injury.[11] Some investigators suggested a potential relationship between JXG/AOX and cytomegalovirus (CMV) infection; however, there is no firm evidence to substantiate such an association.[12] Development of JXG following treatment for T-ALL and LCH in some patients has led to a theory proposing that chemotherapy induces transformation of Langerhans' cells and clonally similar T-lymphoblast leukemic/lymphoblastic precursors into foamy cells.[13,14] Further research has led to the theory that an LCH-induced cytokine storm leads to the development of JXG.[15] Recent evidence suggests that JXG belongs to a group of "inflammatory histiocytic/ dendritic neoplasms," derived from a histiocytic/dendritic stem cell precursor, which is mutated and clonally expanded. This theory is supported by identification of MAPK/ERK pathway mutations in JXG, although BRAF V600E mutations (common in LCH and Erdheim-Chester disease) are not typical of JXG.[16,17]

The treatment of JXG varies and is dependent upon location. While cutaneous JXG typically stabilizes or regresses in one to five years, treatment of periocular and ocular JXG is often required due to potential visual complications if the disease is allowed to run its natural course.[17] Excisional biopsy is a frequent treatment modality for conjunctival and eyelid lesions, which has the advantage of being both diagnostic and therapeutic. Conjunctival and eyelid JXG have also shown response to topical and intralesional corticosteroids.[4,18] Orbital JXG has been documented to undergo complete resolution with excisional biopsy as well as conservative observation.[4,19] Choroidal JXG has been noted to resolve following systemic steroids and radiation therapy. Immediate treatment for iridic JXG is imperative, as studies have shown therapy is required to avoid complications such as iritis, severe hyphema, secondary glaucoma, neovascularization, vision loss and enucleation. High-dose topical corticosteroids with a prolonged taper over three to four months has proven effective in most of iridic JXG cases. For refractory cases, periocular corticosteroids, systemic steroids, excisional biopsy and low-dose ocular radiotherapy (in escalating order) have all shown appropriate responses.[4] Surgical excision is the gold standard for management of AOX. Reportedly, AOX responds poorly to topical steroids; intralesional steroids and/or excisional biopsy are required for disease resolution.[8]

Overall, the prognosis for ocular JXG/AOX is excellent. A review of 30 ocular JXG patients demonstrated tumor regression in all patients following treatment, with only two patients experiencing persistent neovascularization of the iris and elevated IOP.[4] None of the eyes required enucleation. In one review of AOX, all patients (n=10) showed complete resolution without recurrence following excisional biopsy.[8]

In conclusion, JXG/AOX should be considered in a patient with an elevated dome-shaped yellow-orange epibulbar nodule adjacent to the corneoscleral limbus. Clinical-pathologic correlation is required to exclude the potential systemic associations. While the exact etiology of JXG remains unclear, the recent evidence suggests that JXG belongs to a spectrum of inflammatory histiocytic-dendritic neoplasms. Topical/intralesional steroids and excisional biopsy remain the mainstay of treatment for ocular JXG/AOX, with systemic corticosteroids and ocular radio-

therapy being reserved for recalcitrant cases. While most patients experience complete tumor regression without significant visual sequelae following therapy, it's important to monitor patients for recurrence and associated symptoms such as glaucoma, neovascularization and vision loss. REVIEW

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

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

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

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

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

- Hypersensitivity *[see Contraindications (4)]*

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

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

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

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

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

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

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

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

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

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

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Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

T2020-87

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).[3]

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. **Pivotal trial data:** The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study endpoints 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 Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3]

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: ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

Indication

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

Important Safety Information

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

References: 1. US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed April 17, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020.

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