Herpes Management Doesn’t Have to Be Scary

How to nail the diagnosis, use the right drugs—and give patients relief. P. 29

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When Selecting an Rx Treatment for Dry Eye Disease

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

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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.

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When Selecting an Rx Treatment for Dry Eye Disease  

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

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

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

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

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


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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 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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At the recent American Academy of Ophthalmology meeting, the American Society of Retina Specialists presented the results of its most recent Preferences and Trends survey.1 The survey was given electronically to 2,971 members of the society (2,615 regular members and 356 fellows); 1,057 respondents completed the survey (35-percent response rate). The survey is an interesting snapshot of retina specialists’ approaches to various clinical and surgical situations.

The management of age-related macular degeneration is always a focal point of the survey. For wet AMD patients who have a suboptimal response to Avastin (bevacizumab, Genentech) treatment, 88.4 percent of the physicians say they’ll switch to Eylea (aflibercept, Regeneron). A smaller percentage, 11.1, say they’ll switch to Lucentis.

In the course of treating these wet AMD patients, a point that’s often raised is what to do if some fluid still exists, and surgeons were asked their level of tolerance for a small cystic space on OCT in a patient who had long been stable during an eight-week anti-VEGF regimen (the vision is good and symptoms remain unchanged). Most respondents, 68.3 percent, say, “Some cystic spaces may not represent active exudation; might tolerate,” 17 percent say they “usually tolerate small cystic spaces and wouldn’t adjust their strategy,” and 13.7 percent say they have no tolerance for any fluid and that cystic spaces may represent intraretinal fluid, so they’d adjust their strategy.

Los Angeles retina specialist David Boyer says this approach jibes with what he’s seen. “We’ve learned over the years that some of these small cystic spaces are really intraretinal degenerative cysts and aren’t part of leakage,” he says. “If we have a patient with a few of these cysts, it may just be degeneration of the retina and not active leakage. The same goes for subretinal fluid: We try to treat it to dry it out, but we’ll tolerate some small amount of subretinal fluid; it may turn out to be beneficial to the photoreceptors at this point.”

Retina specialists have one eye on the future however, and are interested in new therapies: In response to the interesting question, “In what percentage of your currently treated wet-AMD patients are you (or your patient) actively seeking improved outcomes (e.g., longer duration or improved efficacy) not provided by current anti-VEGF options?” 24 percent say more than half of their patients are looking for improved methods, 22.2 percent said between fully 26 and 50 percent are looking for something new, and 27.7 percent said between 11 and 25 percent are looking for improved outcomes of some sort.

Dr. Boyer says he thinks the number of patients and doctors looking for better options is probably even higher in diabetic retinopathy. “In diabetes, there are many times that I have to switch drugs, add a medication or use a steroid,” he says. “That’s why we’re looking for other treatments with different modes of action. Perhaps Vabysmo may be better; we’re also getting longer-acting steroids and, hopefully, some of the plasma kallikrein inhibitors may improve results in some of the diabetic retinopathy patients with persistent fluid.”

The survey also asked respondents their thoughts on why it appears that real-world research studies often report undertreatment with anti-VEGF agents for wet AMD. The most popular reason given was patient non-
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compliance with visits, at 35 percent, followed by “provider preference for less-frequent treatment” at 28.4 percent. (The other reasons appear in the graph, below right.)

“The reason for [undertreatment in real-world studies] is multifactorial,” Dr. Boyer says. “Patients wear out. They don’t want to come in as often. Study patients are highly reliable and aren’t the average patient. In studies, you’ll see more than 90 percent of people receiving the proper amount of medication. In patients we’re treating, these lesions are often big, and patients will drop out or try to reduce the treatment frequency. A doctor who’s busy may often try to push the envelope and push the injections out an extra week or week-and-a-half. Also, I think a lot of people are using treat-and-extend. So, you have approximately 75 percent of patients who can go three to four months [between injections], so if you look at it compared to the treatments in the studies where you were mandated to administer treatment either monthly or every two months, you’re going to be way under. It doesn’t seem to be economics because Pfizer had the same exact result as the studies that pooled Medicare databases.

“Using the studies as a baseline isn’t the best way of following these patients,” he continues. “It would be best to look at the small studies where they used treat-and-extend and saw the results are good with minimizing the amount of treatment. I think 80 percent of physicians use treat-and-extend.”

A question that often arises in panel discussions, and which also appeared on the survey, is how to handle the diabetic retinopathy patient with peripheral non-perfusion on fluorescein angiography but no neovascularization or diabetic macular edema. On the survey, 45 percent of the respondents said they’d monitor the patient every three months, 26 percent would perform panretinal photocoagulation, 12.6 percent would monitor every one to two months, 9.9 percent would administer an anti-VEGF injection and PRP, 4.6 percent would use an anti-VEGF injection alone, and 1.8 percent would take some other course of action.

“These are patients that a lot of people will follow carefully every three months looking for signs of active proliferation,” Dr. Boyer says. “We see non-perfusion very commonly in these patients, and we haven’t done a study in these patients without neovascularization to see if laser will make a difference. Obviously, however, if you have a non-compliant patient and they’re lost to follow-up—they are getting sick or lose their insurance and can’t come back in a year—they can return to your office and look terrible. I think this type of treatment or observation decision really depends on the compliance of the patient and what their A1C is. If someone comes in and their A1C is 9 or greater, they’re probably not a (Continued on p. 16)
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When your job involves researching ophthalmic topics, interviewing ophthalmologists and writing articles about the profession, you’re often called to drill down deeply into such topics as protocols for treating severe non-proliferative diabetic retinopathy, ways to approach LASIK enhancements or the latest variations of the Yamane suturing technique. However, when you come up for air and attend a social event with family and friends, and someone learns what you do for a living, they almost always immediately ask, “So what are they doing for eye floaters? Mine are driving me nuts!”

These little, innocuous aberrations which, for the longest time, were just viewed as something a patient has to live with, can actually have an oversized impact on a person’s life. A recent article by researchers in Canada published in *BMC Ophthalmology* reported that, of 6,590 primary eye-related visits to general emergency services, 687 (10.4 percent) involved symptoms of flashes and/or floaters. Ophthalmology emergency services needed to be consulted for flashes and/or floaters in 89 percent of cases (608/687). The researchers noted that patients who consulted ophthalmology emergency services waited a total of 1,345 hours in general emergency services and accounted for $81,879.70 CAD in costs.

“In the current framework of care,” the authors wrote, “patients presenting with flashes and/or floaters in general emergency service settings can contribute to service volume, consume health-care resources and spend significant time waiting before their contact with an eye-care provider … .”

In recent years, no doubt as instrumentation and experience have gotten better, retina specialists have taken notice of how much of a problem floaters can be for some patients, and some have begun treating them.

As mentioned in our News section this month, in the most recent Preferences and Trends Survey by the American Society of Retina Specialists, 49 percent of retina specialists perform one to three vitreous-opacity surgeries each month, and 4.2 percent perform four to six. Of course, these surgeries aren’t performed on every patient with an opacity, just ones that meet certain criteria, and patients are informed of the risks inherent to the procedure. Even so, for someone who’s been an interested observer of ophthalmology for decades, it’s interesting to see such a change in attitude.

In the grand scheme of retina therapy, floaters may be a side note; but, to some patients, they can fill volumes. Kudos to retina specialists for recognizing that.

— Walter Bethke
Editor in Chief


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ASRS Survey

compliant patient and you probably want to be more aggressive to prevent vision-threatening complications in the long run. But if their A1C is 7.5 or below, you know they’re somewhat compliant and will come back, so you may want to watch them until they reach a certain threshold. I can’t fault anyone for treating these patients with the idea that if they get lost to follow-up they can do very poorly. On the other hand, I can’t fault someone who says, “I’m just going to watch them until they develop high-risk characteristics and then treat them at that point.”

In something of a sea change, treating patients’ vitreous floaters is no longer taboo. Forty-nine percent of the respondents say they perform one to three vitreous-opacity surgeries each month, 4.2 percent do four to six, 2.1 percent perform seven to nine and 0.8 percent do 10 or more.

Forty-four percent don’t perform them.

“I’m not surprised,” says Dr. Boyer. “In the past, floatectomy surgery was looked at as outside the norm. Now, however, the most common question I’m asked after removing floaters is, ‘When can you do my other eye?’ In these patients who are really bothered, the vitreous gel can, in some cases, reduce their dark adaptation.

“Obviously, it involves risks,” he continues, “but they appear to be minimal if you don’t start doing things like peeling the ILM and all you do instead is just go in and remove it. As surgeons gain more confidence and realize what they’re doing really does help the patient, I think you’ll see this increasing over time despite the fact that it’s surgery. These floaters are really a problem for some people.”


Genentech/Roche Susvimo Implant Recalled

Around this time last fall, the FDA approved the first sustained-release drug delivery system for wet AMD, the intravitreal implant Susvimo (100mg/mL ranibizumab injection, Genentech/Roche), a novel treatment approach requiring a medication refill only every six months. Fast forward to this year and the product is being pulled from U.S. shelves due to a voluntary manufacturer recall relating to a potential leakage problem.

Between twice-yearly treatments, the implant is designed to dispense the anti-VEGF agent into the vitreous in a controlled manner. However, on Oct. 18, Roche CEO Bill Anderson explained in an investor call that, due to a manufacturing issue, the company has cause for concern that there may be a problem with the seal on the intravitreal device that’s intended to prevent the medication from leaking out after it’s injected. As reported in the industry publication, Fierce Pharma, Mr. Anderson communicated Roche’s concern about the possibility that the seal could fail after repeat dosing and is quoted as saying, “because it didn’t meet our performance standards, and [because] we want to make sure that we have high reliability, we decided to voluntarily stop distribution of the port delivery system.”

Roche advises patients who already have the Susvimo implant to continue receiving refills as normal, and notes that explantation is not necessary. However, no new patients will be able to receive the implant until the production issues are resolved and the device returns to the market, which the company estimates will be approximately within a year or so.

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New Thinking on IOL Exchanges

A recent study found no meaningful difference in complications in exchanges with an open or intact posterior capsule.
and in turn the lay public, to believe that once a capsulotomy is performed, there are no good opportunities for IOL exchange.”

We spoke with Dr. Masket and Mr. Alsetri in the days after the AAO meeting to find out more about what their study revealed and how it may influence other surgeons to consider their data.

**Study Methods and Outcome**

The retrospective study included 90 eyes that met their strict inclusion criteria. Any eyes undergoing IOL exchange due to IOL malposition, dislocation or subluxation were excluded, as well as eyes with preoperative uncontrolled inflammation, glaucoma or a visual potential worse than 20/40.

“We only wanted the indication for the exchange to be for optical considerations so we could attribute any complication after the exchange to the exchange itself,” says Mr. Alsetri. “We didn’t want to muddle our data with any complications that could have occurred because of the condition of the eye before the surgery or because of a dislocated lens as well.”

The absence of ocular comorbidities in the study population is what makes this so unique, adds Dr. Masket.

“There were no malpositioned lenses, no bleeding, no complications from prior surgery. The only problems were related to the optical function of the existing IOL; this would include a diffractive optic dysphotopsia, negative or positive dysphotopsia, an opaque lens, or Z syndrome with Crystalenses.

“What was unique about these patients was that they all had good visual acuity, but all had intolerable symptoms related to the nature of the lens. No study has looked at this before,” Dr. Masket says.

“There is far less literature but more misinformation about the risks related to exchanging a lens with an open capsule. We believe that this study gives confidence to the patient that they can be helped and confidence to our colleagues that with proper surgical technique, these cases can gain relief from their intolerable optical side effects of lens-based surgery.”

The main safety outcomes included:

- postop IOP control;
- was their best corrected vision affected by the surgery;
- need for glaucoma drops or procedure(s) to manage postoperative IOP;
- presence of postop retinal edema or anterior chamber inflammation;
- presence of retinal tears or detachments;
- presence of corneal decompensation or edema; and/or
- presence of visually significant vitreous hemorrhage.

“We looked at all of these factors after surgery, and compared them between the two groups,” Mr. Alsetri says. “We found that there were no clinically or statistically significant differences between them.”

In fact, adds Dr. Masket, complications were fortunately low in both groups (Figure 3). “That gives us more confidence that if the surgery is done pristinely then we can expect similar safety profiles when we’re looking at an IOL exchange regardless of the status of the posterior capsule,” Mr. Alsetri says.

The method of fixation for the majority of secondary IOLs was by optic capture in the open posterior capsule group versus bag-to-bag exchange in the closed posterior capsule group (Figure 1).

Secondary outcome measures were postop refractive error. In this area, the research did reveal some differences between the groups. “The one difference that we did encounter was not in regard to complications or final best corrected visual acuity, but in the uncorrected visual acuity, because we found that we were less accurate in predicting the correct IOL power for the secondary lens in the group that had open capsules,” says Dr. Masket.

“We looked at their spherical equivalent after the surgery, and compared it to our pre-surgery intended aim,” says Mr. Alsetri. “We did find both a clinically and statistically significant difference between the two groups in that regard. Our mean difference from aim was -0.7 D in the OPC group, and just -0.41 D
In fact, ~25 million eye care patients are affected by Demodex blepharitis (DB).

We're willing to bet most eye care professionals don't realize just how prevalent Demodex blepharitis is.

DON'T BELIEVE US?

References:

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CHRISTIAN, real DB patient and ophthalmologist
In fact, ~25 million eye care patients are affected by Demodex blepharitis (DB).\(^1\)

We’re willing to bet most eye care professionals don’t realize just how prevalent Demodex blepharitis is.\(^1\)

This emphasizes the importance of setting expectations with the patient, Mr. Alsetri continues. “The surgeons at Advanced Vision Care always have that conversation with patients at the beginning to explain that their best corrected vision is going to be with glasses if they have an OPC, because we can’t guarantee the refractive outcome.

“A lot of these patients opted for diffractive optic lenses at initial surgery as a solution to their presbyopia and now those lenses are being exchanged for standard monofocal lenses. They’re losing the benefits of the lens technology that was initially implanted, as well as the associated negative optical symptoms after the exchange. That can be disheartening to the patient if it’s not explained beforehand,” Mr. Alsetri says.

“Cataract or lens-based surgery is often erroneously compared by the lay public to LASIK outcomes. We can’t be as accurate as LASIK by any stretch of the imagination,” Dr. Masket chimes in. “Patients do need to understand that, while they may have been free of glasses with their multifocal IOL, they may need glasses in some form with the new monofocal IOL.”

He adds that there are literature references that agree that secondary IOLs aren’t as accurate with regard to optical outcomes as in-the-bag IOLs because the lens power formulae were designed for an in-the-bag IOL. “We don’t have refined formulas for lenses that are either fixated to the iris, fixated in the sulcus or scleral fixated, and so we extrapolate based upon how far anterior we think the lens will sit under those circumstances.”

**Figure 3. The study found no statistically significant difference in postoperative complications when comparing the two groups.**

**DISCLOSURES**

Dr. Masket is a consultant and investor for CAPSULaser and Haag-Streit. Mr. Alsetri has no financial disclosures.

Dr. Masket says this study reinforces the feeling he had about patient outcomes. “I sense that this is an important investigation that Mr. Alsetri’s mined data has brought to light and we feel that there is a strong safety profile for IOL exchange,” he says.

Although Dr. Masket and his colleagues are confident in advising patients not to be overly concerned about the added risks of an OPC IOL exchange, they feel the procedure’s safety profile could be further boosted by additional data.

It’s also important to note the experience level of the surgeons whose data was analyzed. This point was raised during the paper presentation session at AAO, Mr. Alsetri says. “The moderator, Nick Mamalis, MD, said results may differ ‘in the hands of mere mortals,’ which is to say that exchanges haven’t always had the best results when it comes to inexperienced surgeons and the open posterior capsule. So there’s definitely a learning curve and a comfort and competence level that’s appropriate to achieve the results that we’re discussing right now,” Mr. Alsetri says.

On an even larger scale, Dr. Masket wants these results to give hope to patients suffering from dysphotopsias and similar symptoms, despite having a successful surgery initially.

“Patients can be highly distressed by dysphotopsia and similar symptoms, yet the eye can be anatomically pristine after surgery that mave have been done beautifully; this is frustrating to surgeon and patient,” he says. “Among the very first things that we tell patients is that if it comes to it, we expect that we can help them surgically. I think it’s very important to let patients know that their life is not over, so to speak.”
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Giving Thanks for
The Lost Holiday

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

There used to be two holidays between Labor Day and Christmas. Of course, you can’t tell these days since as soon as you are back from your long Labor Day weekend the Halloween candy and pumpkin spice lattes are out. And before the first trick or treater knocks on your door, its full-on Christmas in the stores. The poor turkey, or maybe the lucky turkey. Not sure which. What had been the consummate American holiday, ripe with native American poultry and extended family gatherings, has been bowled over by the much sexier and more virulently consumer-driven Yuletide.

Before I go on with my Thanksgiving lament, let me fess up and say I find Thanksgiving painful. While the holiday itself has been run over and its origins debunked, it’s still a notable social gathering in most families. And why not? Who can fault our moms for trying to get everyone together, even if many of us aren’t talking to each other? That’s one of the reasons I’m no fan: The concept of getting together is great, but as the intent of the holiday got lost in the shuffle to New Year’s, it simply became, in large part, another dinner party—in the middle of the week, often at a great distance and with as many of the relatives as you could guilt into coming, even though you didn’t have a lot to say to them. Then we get to repeat it all again in a month. I wasn’t always sure of the point of Thanksgiving, since it just seemed like a dry run for Christmas, but without the good cheer.

By now many of you hate me and think I’m an old curmudgeon. I guess to a degree I am. Lest you think next month’s column is going to see me playing Scrooge, I would refer you to last year’s December column. As that column showed, I love the holidays, whatever you celebrate, and whatever you call them. It’s the underlying concept that should drive how we feel and how we celebrate at this time of year, not a fairy tale of Pilgrims and Native people. So, I’m going to surprise you and advocate for a renewed celebration of Thanksgiving. Emphasis on the ‘thanks’ part. This is especially true this year, the year that was supposed to be a return to calm and normalcy but which is anything but.

I know that in many families there’s a dedicated part of the evening where everyone gets to say what they’re thankful for. It’s a very laudable moment, if not somewhat contrived. I’m advocating for something less “sound bite” and more communally heartfelt. I’m not sure what that is, or how to achieve it, though. It’s one of those ‘I’ll know it when I see it’ things. I do know that it should be a true inner look at who and where we are, the people around us who’ve made a positive impact, and our relative— if not absolute—good fortune. Because, no matter how motivated, hard-working and driven we may be, we don’t exist in a vacuum. None of us got here on our own, nor would it be much fun to celebrate that way.

In a world that looks ever scarier, we should give thanks for all the cliché wonders of living where we do, the freedoms and opportunities we still enjoy, and our relative ease and comfort. Beyond that, look around and identify what makes your thanks personal and unique to yourself, and stop taking your good fortune for granted. As Americans, we generally focus on what’s next, what’s better, what’s missing. It drives us, but it also distracts us from living in the moment, from seeing what we’ve already accomplished and achieved. So, on November 24 and every day, stop for a minute. Look around and smile. And under your breath, say thank you to the world around you.
AcellFX is a human amniotic membrane that provides a protective environment for repair of the cornea and conjunctiva,* allowing re-cellularization to occur and the ocular surface to return to a healthier state\textsuperscript{1-3}

References:

*There are no specific FDA indications for the product.
This information does not guarantee payment and is not legal advice.
It is the provider’s responsibility to check for proper coding and billing.
Before use, please refer to Information for Use (IFU) package insert.
The Scoop on Recent Audit Activity

Medicare auditors are waking up from their pandemic-induced slumber. Here’s how to stay in their good graces.

At the beginning of the COVID-19 Public Health Emergency, CMS reprioritized their audit activity and allowed Medicare Administrative Contractors (MACs) and Qualified Independent Contractors (QICs) more flexibility in their auditing processes.1 As a result, there were far fewer audits of physician practices in 2020 and most of 2021. That hiatus seems to have come to an end. In late 2021 and through 2022, many ophthalmic practices have been, and continue to be, asked to provide medical records to support claims submitted for reimbursement. In this month’s column, we’ll look at the salient points regarding these audits.

What types of audits are currently active?

Ophthalmologists are getting chart requests for Targeted Probe and Educate (TPE) audits, Supplemental Medicare Review Contractors (SMRC), Recovery Auditors (RA) and Unified Program Integrity Contractors (UPIC) auditors.2-5 Many practices have recently received comparative billing report (CBR) letters, but these aren’t audits. The CBR program was intended to enhance accurate billing practices and support providers’ internal compliance activities. A CBR discusses the billing and/or prescribing patterns that may be prone to improper Medicare payments.

Receiving a CBR is not an indication of a current audit or an indication that an audit may be initiated.6 Furthermore, a CBR doesn’t require a response. Also, you can access your CBR online.7

What ophthalmic services are getting the most audit attention?

Cataract surgery and injections—both intraocular injections and botulinum toxin injections—have been the focus of TPE, SMERC and RA audits.

For cataract procedures, these reviews focus on the medical necessity of surgery, as well as the accuracy of the coding on claims. Carefully review your Medicare LCD for cataract surgery, especially the language in the “Indications for Coverage” and the “Required Documentation” sections. Common requirements include patient “Activities of Daily Living” affected by decreased vision, a best-corrected visual acuity and a statement that a change in glasses will provide a satisfactory improvement in vision. Some LCDs also require the use of the VF-8 form or similar questionnaire. Others require a physician attestation stating that other ocular conditions have been ruled out as the source of the decreased vision.

What deficiencies have been seen in reviews related to injections?

Primarily, the reviewers are looking to ensure the billing rules are being followed and the procedures are well documented. Billing-rule issues include:

- the timing of injections; procedures repeated on the same eye within 28 days may be “off label,” depending on the medication used;
- valid clinical indications, diagnosis, test results and clinical findings; and
- minor surgery rules as they pertain to billing an exam on the same day as the injection.

Don’t presume that since these are office-based procedures they don’t require a procedure note. Also, very abbreviated notes are difficult to defend. Appropriate documentation for injections includes:

- a surgical plan including the name of the drug, the dosage, and the indication;
- documentation of physician
GET MORE OUT OF YOUR EYEDROP BOTTLES

Have you ever heard patients complain about their eyedrops? Maybe they ran out before the end of the month and had to wait for insurance to cover their next refill, or their eyes felt flooded with too much fluid? Have you noticed how much of the drop runs down your patients' faces when you're trying to dilate their eyes? That's because eyedrops are too large for the eye to absorb. The Nanodropper Adaptor has solved this problem. Here's how it works.

What's the problem with eyedrops?

They're too big! About five times too big, to be exact. This means 80% of every eyedrop (and thus, every bottle) is wasted due to overflow and/or systemic absorption. This waste contributes to financial barriers to care, and clinical research has shown oversized drops increase both local and systemic side effects!

How does Nanodropper help?

Pretty simple — by reducing the size of eyedrops to just what the eye can absorb! Smaller drops reduce waste and the cost of in-clinic and prescription at-home eyedrops, and research has shown smaller drops minimize local and systemic side effects.

The Nanodropper is compatible with most of your commonly used in-office drops like Phenylephrine, proparacaine, OTC drops like Lumify, and expensive glaucoma medications like Rhopressa, Rocklatan, Vuity, and many more!

“Two of the greatest obstacles to adherence are both price and convenience. The Nanodropper has the potential to minimize both of these impediments. Most commercial drops have a volume between 30 and 50 microliters. By reducing the volume per drop to 10 microliters, the effect of each drop should be the same, yet a bottle would last approximately 3 to 5 times longer. This would not only make medication last longer, obviating the need for frequent visits to pharmacies, but also significantly reduce medication burden on individuals with fixed incomes.”

- Alan Robin, MD, Ophthalmologist, Founding Member of the American Glaucoma Society and Advisor for Nanodropper

Hundreds of clinics nationwide have improved their standard of care. Are you ready to fight back against the eyedrop problem?

The Nanodropper is the only FDA-listed, volume-reducing adaptor for eyedrop bottles designed to deliver precisely the amount of fluid the eye can absorb. Smaller drops reduce the waste and cost of in-clinic and Rx formulations while minimizing local and systemic side effects.

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informed consent;
• a procedure note including the volume and dose of the injected drug, the lot number and expiration date, as well as how much (if any) was wasted or discarded;
• documentation of any complication (including medication errors); and
• discharge or follow-up instructions.

**Q** How should I craft a response to an audit letter?

**A** Organization is key. You should assign one ‘captain’ to oversee the project but you may need to assemble a team to gather the notes and formulate a response. In the event you’re undergoing multiple audits at once, treat each as its own project. This is not uncommon in group practices where the separate records requests are made of each physician.

Carefully read the entire audit response letter—then read it again. First, pay attention to deadlines. Ask for extensions, if given the option. Next, take note of the documents being requested, perhaps create a checklist to be used in gathering and organizing the data. Some requests specify the order in which they want the documents arranged. Send everything the reviewer needs to support the claims in question, even if that includes forms or dates not specified in their request.

If options are provided, determine how the documents will be given: i.e., via an established digital portal; as shipped paper copies; or through a secure email system. Keep copies of everything you send and keep a log of any correspondence (e.g., phone calls, emails, letters) related to the project.

**Q** The SMRC audit response offers a Discussion and Education period. What’s involved with this, and should we agree to it?

**A** The D&E period allows the reviewer the chance to discuss the rationale of their review findings, communicate recommendations and educate the provider on coverage, coding and payment policies related to the services audited. This is done to avoid future denials and provide another opportunity to submit missing documentation. Practices should take advantage of this. The audit-result letter gives you 14 days to submit your request for a D&E. Note: even if you miss this deadline for scheduling this D&E, request one anyway. The SMRC reviewer is likely to agree and schedule the D&E session within 14 days of receiving the request.

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**Q** If our review results are unfavorable, can we appeal the auditor’s decision?

**A** Yes, there’s a standard audit appeal process. This is usually conveyed in the audit response letter you receive. Often, you’re allowed to provide additional information for a re-review. The appeals process usually begins once a demand letter is received. Visit the website for the Medicare Administrative Contractor for its instructions and forms.

**Q** We’ve responded to the request with the appropriate documentation, now what?

**A** Though you might prefer to “sit and wait,” this is a good time to review your work and make changes that may improve your compliance with the billing rules moving forward.

As you prepared your response to the auditor, you may have uncovered areas where improvements could be made in your process or in your team. For example, it may be time to assess current forms, templates, EMR use, billing office procedures or overall revenue cycle process. Make updates as needed. Consider educating, or re-educating, physicians and staff on the importance of accurate documentation and coding. Revisit the role of, and the tasks assigned to, each member of your team, and confirm they’re provided with the tools and resources needed to complete those tasks.

In conclusion, while you can hope your practice never gets audited, that isn’t a management strategy. Instead, practice in a way that you can withstand any payer scrutiny if or when it occurs. To summarize:

• establish a compliance or quality assurance program;
• stay up to date on coding and billing rules;
• review and adhere to payer policies;
• conduct ongoing employee training; and
• monitor your accuracy using internal audit programs.

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**Diagnosis and Treatment of Herpes Keratitis**

With the help of antivirals and steroids, patients can find relief—if the diagnosis is accurate.

**LIZ HUNTER**  
**Senior Associate Editor**

Considering its rate of infection—estimated to be 67 percent of the global population under age 50—herpes simplex will continue to manifest ocularly with a range of complications and risks to patients.

Herpes simplex virus type 1, primarily transmitted by oral contact, commonly infects people as children, with a lifelong risk of symptomatic or asymptomatic viral shedding. In many, HSV-1 will show up as a cold sore or fever blister, but ocular symptoms can present as blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, endotheliitis, iritis, trabeculitis and retinitis.

Herpes simplex keratitis and herpes zoster ophthalmicus each pose significant risk to a person’s vision, making accurate diagnosis crucial to its treatment and ongoing prevention.

We spoke with several cornea specialists about what you should look for in order to properly diagnose ocular herpes and which treatment methods show the most success.

**Making a Diagnosis**

Pain isn’t one of the primary complaints patients will have when it comes to herpes simplex keratitis. “They’ll come in with either red eye, blurred vision or light sensitivity,” says Sonal Tuli, MD, MEd, a professor and chair of the department of ophthalmology at the University of Florida. On the other hand, zoster presents with very distinct skin lesions, redness and swelling, and patients will have a tingling, painful sensation. “It can initially be misdiagnosed as just a rash or an allergy or bacterial infection, but then patients will get these blisters that break down and cause crusting and scarring. Then, it’s pretty obvious it’s zoster,” Dr. Tuli says.

Knowing what to look for during the exam will help you determine the type of virus. “If it’s on the surface of the cornea, this is classically what people see in the textbook as a herpes simplex dendrite. It’s a very specific appearance—you can’t miss it,” says Bennie Jeng, MD, chair of the department of ophthalmology and director of the Scheie Eye Institute at Penn Medicine in Philadelphia.

Epithelial keratitis presents with...
WHAT COULD SHE SEE THIS YEAR?

EYLEA® (aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with Wet AMD.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
• EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

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

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REGENERON

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777 Old Saw Mill River Road, Tarrytown, NY 10591
PROVEN VISUAL OUTCOMES AT YEAR 1 IN THE VIEW STUDIES

Fewer injections with EYLEA Q8 vs ranibizumab Q4

Demonstrated in the largest phase 3 anti-VEGF trials completed to date in Wet AMD (N=2412)\(^1\)\(^-\)\(^3\)

Proportion of patients who maintained vision (<15 ETDRS letters lost of BCVA) at Year 1 from baseline\(^1\)\(^-\)\(^3\).\(^*\)

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<td>EYLEA Q4</td>
<td>95% (12.5 injections(^1))</td>
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<td>EYLEA Q8(^\dagger)</td>
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<td>ranibizumab Q4</td>
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EYLEA was clinically equivalent to ranibizumab.

**VIEW 1 and VIEW 2 study designs:** Two multicenter, double-masked clinical studies in which patients with Wet AMD (N=2412; age range: 49-99 years, with a mean of 76 years) were randomized to receive: 1) EYLEA 2 mg Q8 following 3 initial monthly doses; 2) EYLEA 2 mg Q4; 3) EYLEA 0.5 mg Q4; or 4) ranibizumab 0.5 mg Q4. Protocol-specified visits occurred every 28 (±3) days.\(^1\) In both studies, the primary efficacy endpoint was the proportion of patients with Wet AMD who maintained vision, defined as losing <15 letters of visual acuity at Week 52, compared with baseline.\(^1\)

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

anti-VEGF, anti-vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

ADVERSE REACTIONS

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

INDICATIONS

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


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

The data described below reflect exposure to EYLEA in 1824 patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR), and Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in clinical studies from baseline to week 52 in the combined group of patients treated with EYLEA compared with 4.2% (578 out of 13,704) in the control group.

The most common adverse reactions (≥4%) in the combined group of patients treated with EYLEA compared with 4.2% (578 out of 13,704) in the control group.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across the studies. The anti-VEGF mechanism of action for aflibercept, a recombinant fusion protein containing 55% human and 45% cynomolgus monkey sequences, is based on the ability of binding to, neutralizing, and inactivating VEGF-A, VEGF-B, and PlGF.

The safety and effectiveness of EYLEA in pediatric patients have not been established. There is no information regarding the presence of aflibercept in human milk, the effects of the drug on human milk production, and the potential for the drug to appear 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 infant. EYLEA (aflibercept) injection for intravitreal injection is contraindicated in patients with active intraocular inflammation. The effects of EYLEA on fertility have not been evaluated.
linear dendrites with branches featuring distinct terminal bulbs. To confirm this diagnosis, fluorescein stain should be used for the center of the dendrites and rose bengal on the periphery, says Dr. Tuli. “That’s the classic dendrite staining. The problem with simplex is it doesn’t just cause dendrites—it can cause infection in any of the layers of the cornea, and even in the anterior chamber,” she says. “Those become a little harder to diagnose because the stromal inflammation can be missed. It may manifest as these little hazy patches in the cornea, and if you don’t treat that, then blood vessels can start growing into the cornea and cause pannus or interstitial keratitis.”

Dendrites for HZO look subtly different. “Zoster dendrites, referred to as pseudodendrites, have tapered edges and lack the distinct terminal bulbs,” says Deepinder K. Dhaliwal, MD, LAc, a professor of ophthalmology at the University of Pittsburgh.

Asking patients the right questions can help narrow down the diagnosis. “When you get stromal involvement of the middle of the cornea and you get herpes stromal keratitis, it can be virtually impossible to tell which virus is causing the inflammation because it looks identical,” Dr. Jeng says. “Ask the patient’s history: Have you ever had a dendrite before? Those things can resemble HSK. ESV can show up ocularly via conjunctivitis, dry eye, keratitis, uveitis, choroiditis and retinitis.4 “It’s more likely Epstein-Barr if it’s bilateral, and it involves the stroma at various levels, particularly in the periphery of the cornea. If you present with a deeper infiltrate, we’ll see the Epstein-Barr virus, so being able to exclude herpes simplex serologically has been valuable,” says Dr. Carlson.

If any doubt exists, ordering a herpes PCR is a good idea. Alan Carlson, MD, a professor of ophthalmology and chief of corneal and refractive surgery at Duke Eye Center, says he’ll order a PCR if there’s a question whether the infection is herpetic. “I do recommend obtaining a PCR test, which has replaced the culture, if it’s active epithelial herpes, and if it’s stromal keratitis, I’ll often get a blood test for HSV-1 and HSV-2 because I’ve had several patients now who were able to come off of chronic antiviral medication because they were serologically negative for this virus,” Dr. Carlson says.

This has been helpful especially since Dr. Carlson has noticed an uptick in Epstein-Barr virus, which can resemble HSK. ESV can show up ocularly via conjunctivitis, dry eye, keratitis, uveitis, choroiditis and retinitis. “It’s more likely Epstein-Barr if it’s bilateral, and it involves the stroma at various levels, particularly in the periphery of the cornea. If you present with a deeper infiltrate, we’ll see the Epstein-Barr virus, so being able to exclude herpes simplex serologically has been valuable,” says Dr. Carlson.

If the dendrites don’t have the classic presentation, Dr. Tuli says several factors could cause that, including medication toxicity or a healing epithelial defect. Dr. Dhaliwal says Acanthamoeba keratitis is commonly confused for HSK. “If there’s a dendrite or something that looks like a dendrite in a contact lens wearer and they may or may not have more pain and irritation, we think of Acanthamoeba keratitis before we think of herpes, and the easiest way to make this diagnosis is to remove all of the involved epithelium and just send it to the microbiology lab,” she says. “They can do a PCR for Acanthamoeba and you definitely don’t want to miss the diagnosis of Acanthamoeba because if you catch it early and you remove all the involved cornea, you just cured the patient. It’s really impactful.”

This may come to light during the course of treatment, she adds. “HSK resolves pretty quickly, so if there’s a situation where the herpes isn’t getting better, you’ve got to rethink the diagnosis.”

Diagnosis may be further challenged if the patient has other forms of ocular surface disease, continues Dr. Carlson. “If they have ocular rosacea in addition to viral keratitis, they can be more prone to inflammation and you want to be aware of that because they may require steroids for a longer period of time.”

Treatment Strategies
Once the correct virus has been identified, treatments include oral and topical antivirals, and steroids.

“The treatment for epithelial disease is primarily antivirals,” Dr. Tuli says. “You can use oral or topical, and there’s advantages and disadvantages to each. There’s less resistance to topical antiviral medications because they’re not used globally for other herpes infections, but they can be toxic and patients
might not tolerate them, or children might not tolerate putting in drops every couple of hours. In that case, oral antivirals might be more useful; they’re less toxic and easier to take, but the disadvantage is that it does have to get absorbed into your body.

Acyclovir is often mixed with lactose, she says, so if someone is lactose intolerant they may not absorb it. “People who’ve had abdominal surgeries may not tolerate it, and anyone with liver or kidney failure may not be able to take those medications because they could build up in their body,” says Dr. Tüli. “Deeper infections are typically treated with steroids to calm down the inflammatory reactions, and that often prevents the complications such as scarring and blood vessel growth.”

“Each entity is treated differently,” says Dr. Jeng. “If you see herpes simplex and it’s epithelial disease, then you can either treat it with topical medications or you can treat it with oral medications. Topical medications would include trifluridine or ganciclovir. You can also treat orally with either acyclovir, valacyclovir or famciclovir. If it’s zoster, then there’s been some evidence that ganciclovir might work topically. Orals are also a good choice.”

Dr. Dhaliwal believes topical agents like ganciclovir are “fantastic.” “I don’t typically use Viroptic anymore because it’s preserved in thimerosal and it can have a lot of toxicity,” she says. “I would recommend either using ganciclovir or topical medications for epithelial disease.”

Dr. Carlson tends to avoid the topical antivirals in certain situations. “As somebody that’s in cornea practice, I see a lot of surface disease, so I tend to favor the oral medications based on the safety profile, the cost effectiveness, and the lack of topical toxicity,” he says. “A lot of the topical antivirals are toxic to the surface, so if you’ve got a dry eye or an epitheliopathy or ocular surface disease that’s been made worse by surgery, adding the toxicity of another medication like a topical antiviral could make the patient worse.”

Not to mention, if it’s stromal disease, topical medications don’t work, says Dr. Jeng. “This is a common mistake,” he says. “There are two types of stromal disease: necrotizing, where there’s actually destruction of tissue; and non-necrotizing. Necrotizing suggests that there’s active viral replication, and for that you need to treat with antivirals. If there’s non-necrotizing disease and it’s just inflammation, we treat that with a combination of steroids and oftentimes we cover with antivirals, just in case, but really steroids are the mainstay of treatment.”

Dr. Carlson also uses steroids when dealing with a stromal infiltrate. “I’m a huge fan of topical steroids in that setting and I like to cover with a prophylactic dose of an oral antiviral,” he says. For example, he continues, if a patient had been on 1 g of Valtrex twice a day but no longer has active epithelial HSV, then he would continue the 1 g of Valtrex prophylactically daily and add the topical steroid based on the severity of the inflammation.

But what should you do about treating stromal disease that looks identical in both zoster and simplex? “In zoster we tend to use higher doses because it’s a harder virus, so everything is doubled,” Dr. Jeng says. “For instance, if we’re doing 500 milligrams of valacyclovir three times a day for simplex then we would do 1,000 milligrams three times a day for zoster.”

This high dose of antivirals in the initial zoster episode for at least two to four weeks is going to help
prevent the biggest complication of zoster: postherpetic neuralgia, says Dr. Tuli. “People believe, after the first three or four weeks, that the corneal disease is immune-mediated, and we usually treat that with steroids. At this point, it becomes uncertain if the antivirals actually help with the corneal disease.”

Dr. Dhaliwal personally doesn’t use an antiviral cover for zoster. “Once they get the full oral antiviral dosing of valacyclovir or one of the antivirals then I typically just treat with steroids, even if they have a stromal keratitis or an interstitial keratitis,” she says. “I personally haven’t had any situations where there was melting or problems with this. I’ll use antivirals if there’s a persistent uveitis. That’s another thing that people need to know: herpes-related uveitis is differenti-ated from typical uveitis because you get a higher pressure in the eye.”

The efficacy of using antivirals prophylactically in HZO is the aim of the Zoster Eye Disease Study, co-chaired by Dr. Jeng. Much like the Herpetic Eye Disease Study (HEDS) did in the ’90s for treating herpes simplex keratitis with acyclovir, the ZEDS is doing the same for zoster. The National Eye Institute-supported randomized clinical trial is exploring whether one year of suppressive valacyclovir reduces zoster complications.5

“This is specifically about preventing recurrent disease,” Dr. Jeng says. “If you get an infection in your eye, you can always have more episodes. The question is, if we treat it with low-dose antivirals, will that decrease your chance of recurrence? What the HEDS showed was that for the non-necrotizing stromal keratitis, if you prophylax them with low-dose acyclovir (400 mg twice a day), you decrease your risk of having a recurrent episode by 40 percent. Since this type of disease causes vision loss, it’s important to try to prevent recurrent episodes.”

Many people are under the impression that zoster can be treated the same as HSK to prevent recurrences, says Dr. Jeng. “We just don’t have good data for zoster to support that, and that’s the whole reason behind ZEDS.”

Dr. Jeng expects the study will continue for one to two more years, and the endpoints will look at recurrences at the one-year mark and again at 18 months to see if there’s some sort of lasting effect.

And that’s one of the biggest questions: how do you deal with these patients moving forward?

“Once you’ve resolved their dendrite, what do you do?” muses Dr. Dhaliwal. “Dendrites typically result in scarring and you have to be really careful because they could get recurrent keratitis. I often keep them on a low-dose of antivirals for a long time, and that’s been shown to be relatively safe. The thing that the patients need to know is that the virus lives in the trigeminal ganglion so they’ll never get rid of it; it’s always going to rear its ugly head when they’re stressed out or with UV exposure.”

Final Thoughts

“Herpes is often so confusing to people, but it really doesn’t need to be,” says Dr. Dhaliwal. “Compartmentalize it, so first: is it zoster or simplex? If it’s simplex, is there live virus or not? Taking it step by step is super helpful.”

Returning to her earlier point, Dr. Dhaliwal says, “If it’s not resolving and you have a dendrite in a contact lens wearer, please think of Acanthamoeba keratitis. Unless it’s a classic dendrite, I would have a very low threshold to remove all of the affected epithelium and send it to the lab. That used to be the treatment for herpes, removing the dendrite with a cotton swab and debulking the particles, so even debridement is a treatment as well. It really could be curative, even in both situations, and the worst thing that you did is create an epithe-

CROSS-LINKING: HEADED FOR THE NEXT LEVEL

This vision-saving procedure is on the verge of evolving into multiple new formats. Here’s the latest.

There’s no question that corneal cross-linking has been a miraculous treatment for problems like keratoconus and postsurgical ectasia. But it’s also clear that cross-linking’s earliest protocols have been hard on patients. Today, new approaches to generating cross-linking in corneal tissue are getting closer than ever to becoming real.

Here, surgeons provide an update on several of the most promising new cross-linking variations, including two promising epi-on approaches; miniaturization of the equipment; and triggering cross-linking via an eye drop. In addition, surgeons offer updates on how they’re using cross-linking to address difficult-to-treat infections, and what the outlook is for using cross-linking to treat small refractive errors.

Effective Epi-on: Coming Soon?
Every surgeon involved with corneal cross-linking is well aware that the traditional epi-off procedure is painful for the patient and requires extensive healing time. For that reason, finding an effective epi-on procedure has long been the Holy Grail of the field. Now, two of the systems in development could soon become a reality.

The EpiSmart (epithelium-on) system, from CXL Ophthalmics (Encinitas, Calif.) recently completed a Phase II study for the FDA. The prospective, randomized and controlled study involved 2,228 patients, 1,922 of whom had been diagnosed with keratoconus. The primary endpoint for the study was corrected distance visual acuity, with UCVA, Kmax and minimum corneal thickness as secondary endpoints. Seventy-one percent of patients underwent bilateral, simultaneous treatment (which was possible because there was no need to remove the epithelium).

Study findings included:
• At six and 12 months, keratoconus patients showed improved CDVA, UCVA and Kmax. Minimum corneal thickness was unchanged.
• At six and 12 months, keratoconus patients showed significant improvements in CDVA, UCVA and Kmax ($p<0.001$). These improvements were shown in a prior study to be stable two years after the treatment.
• Minimal corneal thickness wasn’t reduced at any point after treatment, confirming the results of prior publications.
• No bandage contact lenses were applied and patients experienced only brief discomfort, returning to normal activities the next day.
• Only six out of 2,228 patients (0.3 percent) developed corneal haze or opacity post-surgery. (Haze or opacity is reported in 64 percent of those treated with the current FDA-approved epi-off procedure.)

Roy S. Rubinfeld, MD, MA, medical director at Re:Vision in Rockville, Maryland, and Fairfax,

This article has no commercial sponsorship.

Dr. Rubinfeld has equity interest in CXL Ophthalmics. Dr. Chuck is co-founder of TECLens, creator of the CXLens. Dr. Ambati is the president and co-founder of Veeoa. Dr. Balidis is a consultant for Glaukos/Avedro. Drs. Behndig and Kramer report no financial ties to anything discussed in this article. (Dr. Rubinfeld can be reached at Doctor@revisedeye.com.)
Virginia, and a clinical professor of ophthalmology at Georgetown University Medical Center in Washington, DC, is the inventor of the EpiSmart system. “In 2008, while spending time in Europe, I became interested in crosslinking, which was already available there,” he explains. “Right away I was taken with the challenge of finding a way to get adequate riboflavin into the corneal stroma without removing or disrupting the epithelium. I worked on the problem for several years, with input from many exceptionally smart, experienced individuals. By 2011 we’d developed and filed patents on three key innovations.

“It was clear from our early testing that our new approach could be performed quickly, safely and in a bilateral, simultaneous procedure,” he says. “When I first started doing epi-off cross-linking, as part of an IRB-approved study, it was so painful and difficult for patients that my staff hated being part of it, and many patients didn’t even return to have the second eye done. With the new procedure, our patients are back at work or school the next morning. No bandage lenses are used, and we’ve gotten the UV treatment itself down to 20 minutes.”

Another epi-on system currently undergoing clinical trials is the iLink system from Glaukos/Avedro. The Epi-off version of the system is currently FDA-approved, but the epi-on version, which uses their proprietary Epioxa formulation, just completed its Phase III trial.

The company reports that Epioxa achieved its primary efficacy outcome in the Phase III trial by demonstrating a Kmax treatment effect of -1 D (p=0.0004) at six months, prospectively defined as at least square mean Kmax change from baseline in treated subjects compared to those treated with placebo. In the treatment arm, Kmax improved by 0.2 D; the subjects treated with placebo experienced a worsening of 0.8 D.

The company also notes that 98 percent of the subjects randomized to placebo elected to cross over to the Epioxa treatment. Those switching to Epioxa showed an improvement of 0.3 D after six months of treatment. The majority of adverse events were mild and transient. No change in endothelial cell counts was observed.

Epi-on: The Science

“To make epi-on crosslinking effective you need the correct amounts of the three key reagents—riboflavin, UV light and oxygen—in the stromal microenvironment at the same time,” Dr. Rubinfeld explains. “Until recently, no epi-on system has been able to adequately load the stroma without epithelial disruption or the use of iontophoresis. One key innovation in the EpiSmart system that enables epi-on riboflavin loading is the sodium iodide in our formulation.” This increases epithelial permeability without disrupting the epithelium.

“Another stromal loading innovation is the patented disposable sponge applicators, which have unique shapes and physical and hydration characteristics,” he continues. “The first applicator is hydrated with BSS or anesthetic drops. This removes the lipids sitting on the surface of the cornea, so that some of the barrier to loading of the stroma is removed, but it doesn’t disrupt the epithelium. Then another sponge loaded with the Ribostat formula is placed on top of the cornea to act as a loading depot. When riboflavin is delivered in drops, the drops often roll right off the cornea, but with the loading sponge, that doesn’t happen.

“After loading, the surgeon looks at the cornea using the slit lamp to confirm that the green riboflavin is adequately and evenly distributed across the stroma,” he says. “This type of slit-lamp grading has been validated with lab tests such as HPLC and mass spectrometry.”

Dr. Rubinfeld notes another positive effect of having sodium iodide in the formulation. “It helps prevent UV light from photodegrading the riboflavin into inactive materials that don’t assist in crosslinking,” he explains. “If any hydrogen peroxide is formed, for example, the sodium iodide turns it back into oxygen and water, fueling the cross-linking reaction and avoiding toxicity.” Since oxygen is the rate-limiting reagent, this helps optimize oxygen availability in the stroma and avoids the highly variable blocking of UV transmission into the stroma, sometimes called the ‘sunscreen effect.’

“Yes, you can’t get oxygen into the cornea when there’s riboflavin on the surface and the UV light is on,” he points out. “In that situation, the added riboflavin photodegrades and ‘burns up’ the oxygen at the

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Not having to remove the epithelium is an obvious boon for patients undergoing cross-linking, because removing the epithelium is painful and requires a lengthy recovery. However, leaving the epithelium undisturbed also reduces adverse events significantly.
surface. For that reason, no riboflavin drops are used during the UVA application in our protocol.”

Dr. Rubinfeld says another innovation involves the UV light. “Using a UV light that’s constantly on actually undercuts the photochemistry of the process,” he explains. “When the UV light is on, oxygen (the rate-limiting reagent) is being depleted, hypoxia is created and you end up with a toxic stew of hydrogen peroxide and other toxic molecules. Having the light turn on and off at the correct cycling time allows the oxygen to rediffuse through the cornea, replenishing oxygen while it’s off. The total amount of UV radiation is also reduced because the light is only on half the time.

“We’re now on the precipice of initiating our Phase III trial,” Dr. Rubinfeld concludes. “Based on the numbers from Phase II, we feel very good about the Phase III trial.”

The CXLens: Cross-linking on the Eye

While many researchers are primarily focused on improving the cross-linking procedure by allowing the epithelium to remain intact or finding ways to customize the result for keratoconus patients, one company, TECLens (Stamford, Connecticut), has developed an on-eye crosslinking system that uses scleral contact lenses, fiber optics and ultrasound to deliver the UV in a very controlled, targeted manner. The company believes this will eventually realize its long-held goal of pushing crosslinking beyond keratoconus into refractive correction for healthy eyes.

Roy S. Chuck, MD, PhD, chair of the Department of Ophthalmology and Visual Sciences at Albert Einstein College of Medicine in

![Image](image_url)

A key challenge for creating epi-on cross-linking has been getting the necessary amount of riboflavin through the epithelium, without disrupting it, to make successful cross-linking possible. The EpiSmart system’s formula, RiboStat, has demonstrated in clinical trials that it can accomplish this.

Dr. Chuck notes that this approach would be titrated to a patient’s specific needs.”

Dr. Chuck explains that a contact lens reservoir is also used to apply the riboflavin to the eye. “You fill the vault space of the lens with riboflavin solution and place it on the eye for 20 to 30 minutes,” he says. “After riboflavin instillation, the reservoir lens is removed and the UV delivery lens is placed on the eye.” He adds that the CXLens process leaves the epithelium on. “It doesn’t seem to negatively impact the quality of the results, as long as you understand the interaction of the light and the riboflavin, and compensate for the drug that’s in the intact epithelium,” he says.

“During the TECLens procedure, patients can sit upright or lie down, whichever is most comfortable,” he points out. “TECLens’ scleral-lens patient interface allows both eyes to be treated simultaneously with different dosing specifications, saving time for both patient and practice. Additionally, because full-time technician support isn’t necessary, a single operator can treat multiple patients at the same time, further increasing practice efficiency.

“In our pilot study in keratoconus, we used the 375-nm UVA light for 30 minutes to deliver a total dose of 7.2 J/cm² to the central region of the cornea that contains the cone,” he explains. “For refractive correction, the treatment times will be likely be shorter, as the amount of crosslinking would be titrated to a patient’s specific needs.”

Advantages of Miniaturization

Dr. Chuck notes that this approach has accomplished several things. “First, it makes the treatment less expensive,” he says. “Second, it’s more comfortable for the patient.
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Third, the scleral contact lens maintains the positioning of the light relative to the eye.

“In a traditional treatment, if you’re on the table underneath the lamp and you move out of position, the illumination is no longer aimed correctly,” he points out. “For keratoconus therapy, some small amount of patient movement can be tolerated, but for refractive correction, mis- targeting could cause unacceptable errors. The lamp-based systems try to compensate for patient movement by putting trackers in the system that turn off the light if the patient moves. But when you put the light on a scleral contact lens that sits on the eye, if the eye moves, the device moves with it. It becomes an ambulatory procedure. In fact, our clinical procedures were done in the exam room chair.”

Dr. Chuck explains that the first human study was recently done to ensure that the form, fit and function of the device is ready for healthy eyes. Ten patients with advanced keratoconus were treated. “It was a challenge to get some of the later patient visits done, given pandemic shut-downs,” he notes. “However, we were able to complete the pilot trial, and it confirmed that the system works well, is safe, and treats keratoconus effectively, as expected. The data were published last year in Translational Vision Science & Technology. Now we’re in the planning stages for our initial refractive studies and the larger keratoconus trials for approval.”

Dr. Chuck says the company has been working on several additional modifications that might enhance the CXLens system in the future, including a proprietary riboflavin formula intended to increase penetration through the cornea, and a highly oxygenated wetting fluid. In the meantime, it turns out that the results using standard elements such as commercially available riboflavin have been very good.

“Having sufficient oxygen is im-

The CXLens performs cross-linking via a contact lens placed on the eye, which the company says increases patient comfort and eliminates the need for eye tracking.
address the biochemical or genetic causes of the disease. “The cornea is living tissue that remodels,” he points out, noting that this makes regression a very real possibility. “Cross-linking just strengthens the tissue that’s present at the time of treatment. Because surgery isn’t curing the disease and comes with associated risks, trying a pharmacologic treatment first could make very good sense.”

Dr. Ambati believes that this approach wouldn’t eliminate the need for other forms of cross-linking treatment. “I think this drop would expand the pool of potential treatment candidates,” he says. “Keratoconus can range from mild to severe disease. If a patient isn’t ready for surgery or has concerns about surgery, this could be a great option.”

Dr. Ambati notes that if the drop is eventually approved, it’ll be up to the physician to decide what treatment to try first. “There could be patients for whom the drop doesn’t work, or patients for whom you want to do Intacs at the same time as cross-linking,” he points out. “There might be patients who are allergic to the drops or don’t want to take them. Like glaucoma, keratoconus is a chronic disease with both medical and surgical options. It’s up to the physician to figure out which option is best for which patient.”

In terms of what’s next, Dr. Ambati says Glaukos will be planning the next trial. “The Phase I/IIa has been done, testing safety and efficacy,” he says. “The FDA essentially gave us the green light to proceed with two randomized, controlled, Phase III studies. Now that Glaukos has licensed the drop, they can move the ball forward.”

Cross-linking to Treat Infection

Brent Kramer, MD, a cornea specialist at Vance Thompson Vision in Sioux Falls, South Dakota, has some experience using cross-linking to address corneal infections, including bacterial, fungal and Acanthamoeba keratitis. “Of course, I still defer to standard-of-care treatments such as drops, and sometimes when treating fungal and Acanthamoeba keratitis I use oral agents as well,” he says. “But for recalcitrant cases, it’s a tool I have in my toolkit if nothing else seems to be working.”

Dr. Kramer says that cross-linking for infection works two ways. “First, it attacks the bugs at the DNA and cell-wall level,” he says. “Second, you’re theoretically strengthening the cornea by forming covalent bonds.”

“The data out there on this use of cross-linking is somewhat mixed,” he notes. “Patients I’d consider this for have fairly progressed disease and would likely need a corneal transplant in the future. But in those dire situations, the goal is to stabilize the cornea and avoid a therapeutic penetrating keratoplasty while the eye is hot and there’s an active infection. Treating the infection with cross-linking may decrease the risk of corneal perforation, although the jury is still out.”

“That being said, the key to success in these cases is being aggressive about nailing down a diagnosis,” he continues. “Usually, if I can get a firm diagnosis with a culture or by other means, we’re able to treat with drops or oral medications effectively. I wouldn’t use cross-linking as an alternative to the standard therapies; I’d use it as an adjunct therapy when we need to slow the disease process down and we appear to be losing ground every day.”

“Of course, it’s not for everyone,” he says. “First of all, patients who have any sort of herpes simplex aren’t good candidates for this, because we know that UV light can increase the activation of the herpes simplex virus. Even if the patient only has a history of HSV, I don’t think this would be a good treatment choice. Second, if the patient has a very deep infiltrate, I don’t think the UV light/riboflavin combination penetrates deep enough to get a completely effective treatment.”

“Nevertheless, whether this will become a more mainstream approach probably depends on how the technology evolves,” he says. “It could become a very useful treatment when patients are unable to be compliant with drops, or are in parts of the world where drops aren’t available and can’t be compounded. Even here in the United States there are supply-chain disruptions. I think every cornea specialist has had a hard time getting their hands on natamycin for fungal keratitis cases in the past few years. In the future, cross-linking, or something similar could be a potential alternative treatment in these cases.”

“The other issue is resistant bugs,” he adds. “I recently saw a
Feature  CROSS-LINKING

DOES EVALUATING CROSS-LINKING WITH KMAX MAKE SENSE?

The current efficacy metric for cross-linking, commonly used to decide whether or not a treatment has worked, is the cornea’s Kmax value, the steepness at the steepest point on the cornea.

“Michael Mrochen, PhD, once told me that the use of Kmax to evaluate the effectiveness of cross-linking may have begun with an early meeting he had with the FDA,” notes Roy S. Rubinfeld, MD, MA, medical director at Re:Vision in Rockville, Maryland, and Fairfax, Virginia, and a clinical professor of ophthalmology at Georgetown University Medical Center in Washington, DC. “The FDA asked how he had determined whether a cross-linking treatment was effective. He said his group was using the less-than-ideal method of measuring Kmax, which he strongly recommended not using.

“The problem is that Kmax and quality of vision aren’t well correlated,” he continues. “It was my wife, an epidemiologist by training, who first pointed this out to me in 2010. I’d explained that we were using Kmax to determine whether a cross-linking procedure had succeeded. She looked over the numbers and pointed out that there was no correlation between vision improvement and Kmax. Since then, others have confirmed this. In one of our papers, Doyle Stulting, MD, demonstrated that patients who would be considered a failure because they had increased Kmax had mostly gained vision.2 Even Peter Hersh, MD, who did the studies for Glaukos/Avedro has noted that there’s no correlation. This is why our Phase II study of EpiSmart used corrected distance visual acuity as the primary study endpoint, with UCVA, Kmax and minimum corneal thickness as secondary endpoints.”

Dr. Rubinfeld admits that the use of Kmax to gauge the effectiveness of cross-linking may take some time to fall out of common use. “Many patients have been sent back to me by the referring doctor,” he recalls, “with a note saying, ‘The patient’s Kmax is worse!’ I have to point out that the patient has gained three lines of vision. We have a disease that causes people to lose vision, so shouldn’t the metric for treatment success be whether the patient has lost or gained vision?”

—CK

patient with a pan-resistant Pseudomonas ulcer. By the time we’d seen the patient and obtained sensitivities there wasn’t much we could do. The patient eventually lost the eye. But if the resistance of the bug had been detected earlier, cross-linking might have made a difference.”

Refractive Correction

Because cross-linking reshapes the cornea to some extent, it was clear early on that there might be some potential to treat a small amount of refractive error using this technology—especially if the treatment could be customized for each patient. Glaukos/Avedro has produced a version of this treatment called PiXL, which incorporates their Mosaic device. PiXL allows customized delivery of different amounts of light and energy to different areas of the cornea. (PiXL is available in parts of Europe, but not approved in the United States.)

Many surgeons have expressed skepticism about this use of cross-linking, given that the refractive change created by cross-linking is inherently small and the resulting changes in corneal tissue are not yet predictable enough to make a precise refractive change possible. Some of the studies published in recent years shed some light on this idea’s potential:

• One study published in 2020 found that in healthy individuals age 25.6 ± 3.6 years of age with low myopia, treating a 4-mm zone in a high-oxygen environment led to a significant improvement in UCVA (-0.45 ± 0.27 LogMAR) and MRSE (+0.99 ± 0.44 D) at one, six and 12 months.19 (At 12 months post treatment, endothelial cell count and BSCVA were unaltered.)

• Another study, published in 2021 compared two different customized PiXL treatment zones, a homogeneous 4-mm zone and a 4-mm annular zone.20 Similar improvements in UDVA were seen for the homogeneous and annular protocols at one month: -0.52 vs. -0.49 LogMAR (p=0.91). Both groups also showed a similar mean improvement of 1 D in MRSE (p=0.17). Reduction in mean keratometry was -0.8 D and 0 D respectively (p=0.001). The treatment effect remained stable throughout 24 months. No adverse events were reported, but at one week, participants reported less ocular discomfort with the annular protocol.

• A third randomized, single-masked study involving 27 patients (54 eyes), was reported in 2022.21 This study compared two different PiXL protocols. One eye was treated in a central annular zone of 4 mm (UV light 30 mW/cm², with the light on for one second, off for one second); the fellow eye was treated in a 3.5-mm annular zone (45 mW/cm², half a second on, one second off). Results were assessed through a 24-month follow-up. Findings included:

— The 3.5-mm protocol produced a larger improvement in UDVA: 0.52 vs. 0.38 logMAR, p=0.003, and in MRSE: +1.25 D vs. 1 D, p=0.037.

— A transient reduction in LCVA was larger with the 3.5-mm protocol (p<0.01).

— No reductions in ECC or BSCVA were noted.

— The 3.5-mm protocol rendered less subjective ocular discomfort post-treatment.

— No adverse events were noted.

One surgeon who has some experience performing the PiXL treatment is Anders Behndig, MD, a professor in the Department of Clinical Sciences and Ophthalmology at the Umeå University Hospital in Umeå,
Institute of Ophthalmology &

Dr. Behndig notes that so far, his group has only used the PiXL treatment protocol in randomized clinical trials, not in clinical routine. “For a select group of patients with low grade myopia—between -0.75 D and -2 D—the results can be comparable to those of other possible treatments,” he says. “Right now, the effect of PiXL is limited; we had difficulty getting more than 2 D of effect. The precision of the treatment may be another issue, although that’s not a major problem if you select the right patients.”

Miltos Balidis, MD, PhD, a current Mosaic/PiXL user at the Institute of Ophthalmology & Microsurgery Ophthalmica Eye Clinic in Thessaloniki, Greece, has participated in trials relating to treating myopia and presbyopia. “With the tested treatment protocol, we’ve successfully treated low myopia up to 1.25 D,” he says. “Unfortunately, the response to treatment was variable. It didn’t work in every case. And so far, the results using current presbyopic treatment profiles have been disappointing.”

Refractive Correction with the CXLens

The CXLens on-eye cross-linking system (described earlier) also plans to eventually perform cross-linking-based refractive change. To make that possible, the scleral lens UV delivery system also incorporates a tiny ultrasound transducer that can provide real-time measurements of the changes in the cornea produced by the treatment.

“One of the challenges of this type of treatment is the difficult-to-predict corneal response,” Dr. Chuck, co-founder of TecLens, the company developing the CXLens, points out. “The problem is that every eye is a little different; you can put the same illumination on two different eyes and get two different effects. The way to eliminate this variability is to directly measure the biomechanical changes that are happening in the cornea during the treatment. That’s what our ultrasound monitor can do: track the changes in the cornea, in real time, as the illumination proceeds.

“There have been other attempts to do this,” he continues. “One that seems to have fallen out of favor involves using an optical monitor to measure Brillouin scattering. You shine a light on the cornea and monitor tiny changes in the light’s wavelength to determine how the cornea is changing. The major drawback of that approach is that it can’t be done in real time. Using ultrasound, each pulse takes microseconds, and with the device positioned inside the contact lens, you can monitor the corneal changes in real time. This data allows the clinical treatment to be coupled to a computational pre-plan customized for each patient’s topography and underlying corneal biomechanics. That’s been the great hope for cross-linking since the early days; precise control of the reshaping, instead of just doing the procedure and hoping for the best. We believe our system has all the tools to make this happen for a huge number of patients seeking refractive correction.”

Dr. Chuck says that so far the company has successfully used the embedded ultrasound monitor in the lab, using human donor corneas. “It hasn’t been validated in the clinic yet,” he notes. “We hope to do that soon. We look forward to making CXL refractive correction a real option for patients, without having to remove tissue, cause pain, cause post-LASIK ectasia, subject patients to LASIK smoke, and so forth.”

There are numerous artificial intelligence algorithms in the works for glaucoma, from disease detection tools to progression forecasting models. Experts say it will take considerable effort to introduce advanced AI models into the glaucoma clinic, but they agree that AI’s potential for improving patient care and addressing inequalities is very real.

In this article, AI innovators and experts discuss the obstacles to AI development for glaucoma, current research and what’s on the clinical horizon.

A Matter of Consensus
There are certain challenges related to glaucoma that can make it particularly difficult for AI to diagnose and detect. “When you see signs of diabetic retinopathy in a fundus photograph, there’s hardly any question about whether the patient has it or not,” says Felipe Medeiros, MD, PhD, the Joseph A.C. Wadsworth Distinguished Professor of Ophthalmology, vice chair for technology and professor of biostatistics and bioinformatics at Duke University School of Medicine. “Human grading of fundus photographs can serve as a reliable gold standard for DR diagnosis. This makes it easier to develop AI models that can be trained to recognize diabetic retinopathy on a photograph, but glaucoma isn’t quite like that. It may be a tricky disease to diagnose in the early stages.”

Glaucoma is characterized by retinal ganglion cell death, axon death and subsequent excavation of the neuroretinal rim. However, optic nerve head size varies greatly among individuals, ranging from 2.10 mm to 2.35 mm, which makes disease detection tricky. Disc size also varies by age and ethnicity.

“If you show an optic nerve image to different experts, it’s likely that they’ll disagree whether it’s glaucomatous or not, especially in early stages of the disease,” he continues. “Graders tend to over- or underestimate glaucomatous damage and have low grading reproducibility and poor agreement. Therefore, training AI models to predict subjective gradings is problematic.”

In the case of fundus photo analysis, if images are deemed ungradable, i.e., the expert readers couldn’t come to a consensus, then those images are usually excluded from the training sets, points out Sophia Ying Wang, MD, MS, an assistant professor of ophthalmology and a glaucoma specialist at Stanford University. “This...
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may hinder the algorithm’s ability to recognize glaucoma in real-world datasets,” she says. In fact, a study using visual field data found that including the unreliable visual fields improved the algorithm’s predictive performance of future visual field mean deviation.5

Experts say glaucoma’s lack of consistent objective diagnostic criteria may explain why AI in glaucoma hasn’t achieved as widespread an application as AI in retina or cornea. This problem has generated questions about how best to diagnose and detect glaucoma using AI and how to train these AI models.

Since there’s no consensus definition of glaucoma yet, AI investigators devise their own definitions to classify disease into categories such as “suspect,” “certain,” “referrable glaucomatous optic neuropathy,” “probable” or “definite.”6 Dr. Wang points out that using binary definitions of glaucoma such as “probable/definite” may catch advanced cases but limits the detection of early cases, while terms such as “referrable” may be useful when there are too many false positives. “Multiple groups attempt to predict similar outcomes in different ways, and this reduces the ability to compare performance between studies,” she says.

A large, international, crowdsourced glaucoma study on patient data and grading is currently under way, led by researchers at Dalhousie University in Nova Scotia. The Crowd-Sourced Glaucoma Study aims to identify objective criteria on visual fields and OCT that match glaucoma specialists’ assessments of disease likelihood.7 The study spans 15 countries from five continents. Dr. Wang participated as one of the expert graders. “It’s a very exciting way to both collect glaucoma patient data and collect grader ratings to assess inter-rater reliability,” she says.

“In addition to a clinical definition, we also need a so-called ‘computable’ definition, using the data elements that we commonly have in the data-sets that we use for AI studies, such as EHRs,” Dr. Wang says. “This is so that AI algorithms can be compared with each other, or even validated in different datasets. Standardizing and harmonizing definitions of glaucoma is especially tricky as available data elements from health records can vary in different settings and studies. AI work goes hand-in-hand with developing data standards.”

Consensus-defined glaucoma will be necessary to confront the growing prevalence of the disease and the need for large-scale screening. Dr. Medeiros says an effective screening model for glaucoma must be inexpensive, widely available, highly accurate and easy to administer.

The imaging systems required for glaucoma detection are expensive, and trained technicians are needed to operate them. Most community screening locales, such as primary care offices and community centers, don’t have such devices. While there are less expensive ways of imaging patients, such as with smartphone or other handheld retinal cameras, these modalities aren’t as powerful as tabletop systems. Additionally, Louis R. Pasquale, MD, a professor of ophthalmology at the Icahn School of Medicine and in practice at the New York Eye & Ear Infirmary of Mount Sinai, notes that the variability in quality of different fundus cameras, from tabletop devices to smartphone cameras, is going to affect an algorithm’s generalizability.

Different devices also can’t use the same algorithm. “Just as the results from one OCT machine can’t be directly compared to those of another, an AI model trained on a Spectralis machine might not perform the same way in a Cirrus,” Dr. Pasquale says.

Data Availability

Large amounts of data and centralized data registries will be indispensable for training and validating algorithms, experts say. “You can’t train an AI algorithm with only 100 patients,” Dr. Pasquale says. “Once you get an algorithm that works, then you need to ensure it doesn’t go off the rails and become incorrect over time. You need large datasets and constant surveillance to maintain the functionality of an AI algorithm.”

In addition to the fact that large, centralized datasets aren’t widely available yet, sharing the existing data isn’t easy either because of institutions’ differing data privacy policies and the confidential nature of healthcare data in general. “As we build more generalizable algorithms, we need to improve the diversity of our training data and validate algorithms externally,” Dr. Wang says. “It’s difficult to share health data among sites. Right now, there’s a lot of work developing training methods that allow algorithms to be trained on different sites’ data but without exchanging the data. This is called federated learning. It can help to address issues of data privacy, security and access.”

Generalizability

It’s important to have a good understanding of how AI models are developed in order to understand their limitations, says Dr. Medeiros. “Before clinicians use, say, a prediction model, they should understand how the algorithm was developed, the population it was trained on and that population’s characteristics,” he says. “It’s really no different than any medical test. When you’re using a medical test in your clinical practice, such as an OCT or visual field, you need to know the test’s properties and the characteristics of the normative database so you can rely on the results and determine whether they’re applicable to your patient.”

Algorithms trained on one kind of patient aren’t necessarily generalizable to other kinds of patients. For instance, an algorithm trained on a Chinese population might contain a large number of high myopes and therefore be unsuitable for use in a population with different ocular characteristics.

“Generalizability is important if there’s a discrepancy between the population you wish to deploy your
algorithm on and the population you trained your algorithm on,” Dr. Wang says. “As an aside, one could argue that not all AI algorithms have to be universally generalizable if you were planning to train and deploy locally in your own unique population. In fact, it’s much harder to develop one algorithm to rule them all, and I don’t think that’s necessarily a goal we want to have, especially as we enter the era of precision medicine.

“We have to be really careful when we train models to ensure we aren’t training them on inherently biased data and perpetuating that bias,” she continues. “For instance, if we try to predict how sick someone is based on how many medical claims they have, this number may be different among minorities for reasons such as unequal access to care.

“As we enter the deployment phase, we also need to be aware of any differences between the training population and the people we’re using the model on. If the algorithm’s performance isn’t as good in a certain subgroup of patients, it will negatively impact that group and refer them for treatment inappropriately.”

Current Research
In traditional studies, researchers attempt to arrive at some kind of scientific truth. In AI studies looking at prediction or classification, the algorithm’s prediction performance is paramount, notes Dr. Wang.

There are numerous AI studies in the glaucoma space right now, with algorithms for several applications, from detecting structural changes in the eye to predicting which patients might rapidly worsen. Here’s some of the current and ongoing research:

- Using fundus photos to identify glaucomatous eyes. In 2017, researchers trained a deep learning system to evaluate glaucoma using 125,189 retinal images. The algorithm’s performance was validated on 71,896 images. It reported a prevalence of 0.1 percent, with an area under the curve of 92.6 percent vs. ophthalmologists’ 69.6 to 84.9 percent. The best-case consensus scenario area under the curve was 89.1 percent. The algorithm’s sensitivity was 83.7 percent and the specificity was 88.2 percent, compared with 81.3 to 81.6 percent sensitivity and 90 to 94 percent specificity for ophthalmologists (intraobserver agreement 0.62 to 0.97 vs. 1.00 for Pegasus). The correlation between observations and predictions was 0.88 (p<0.001; MAE: 27.8 µm). The researchers noted the algorithm could determine classification in 10 percent of the time it took ophthalmologists. They suggested the tool could be valuable for screening patients.

- Predicting OCT metrics from fundus photos. Dr. Medeiros’ group has developed a machine-to-machine AI model that was able to objectively predict complex OCT metrics such as nerve tissue thickness from a fundus photograph to be used for glaucoma diagnosis. Machine-to-machine learning enables devices to exchange data without requiring human input for network training.

On a test set of 6,292 pairs of fundus photos and OCTs, the mean predicted RNFL thickness was 83.3 ±14.5 µm and the mean observed RNFL thickness was 82.5 ±16.8 µm (p=0.164) with strong correlation between the two (r=0.832; p<0.001). Fundus photography has been an underused resource in the OCT-heavy glaucoma subspecialty, experts point out, but AI is beginning to change that. “The algorithm is quite powerful, and we’ve shown it’s able to detect disease and predict damage by detecting changes in the structure of the eyeball.”
and progression over time,” Dr. Medeiros says. “From a disease-detection standpoint, using a low-cost imaging method such as photography could benefit patients in locations where there’s less access to care.”

**Incorporating multiple modalities.** Dr. Medeiros says his group is also working on integrating multiple imaging modalities and using AI to recognize patterns of damage on OCT instead of relying on summary parameters to diagnose glaucoma.

“There’s much more to an OCT image than the summary parameters,” he continues. “AI models that have been developed and ones we’ve published on are able to perform a much more comprehensive evaluation of the image for glaucoma assessment and diagnosis, as well as recognize artifacts and segmentation errors. This is very important because OCT is only as good as the scan quality. Incorporating AI models into the current software will help flag artifacts and errors with greater accuracy, and technicians acquiring scans could re-scan right away.”

**Assessing the optic disc.** In a cross-sectional study on quantifying neuroretinal rim loss, 9,282 pairs of optic disc photographs and SD-OCT optic nerve head scans from 927 eyes were used to train and validate a deep-learning convolutional neural network to predict BMO-MRW global and sectoral values. The algorithm could quantify the amount of neuroretinal damage on the photographs with high accuracy using the BMO-MRW as a reference, Dr. Medeiros’ group reported.

**Mapping structure to function.** Using SD-OCT to image the RNFL provides more data than red-free RNFL photographs, researchers noted in a 2020 JVIS study. They used a convolutional neural network trained to predict SAP sensitivity thresholds from peripapillary SD-OCT RNFL thickness in glaucoma patients to generate topographical information about the structure-function relationship from simulated RNFL defects. They reported the AI-generated map provides “insights into the functional impact of RNFL defects of varying location and depth on OCT.”

**Creating clinical forecasting tools.** “Currently, we arbitrarily pick a target intraocular pressure based on patient age, how much damage is present, and the IOP level associated with the damage,” Dr. Pasquale says. “But if the patient were identified as a red flag for fast progression by a validated artificial intelligence algorithm, we might choose a lower target IOP to prevent significant vision loss.

“Currently there’s no such algorithm [in the clinic] because it takes considerable time and effort to build; however, I’m very hopeful and excited that those algorithms will be available in the future.”

Developing a clinical forecasting tool might involve training an algorithm on patient data such as optic nerve photos, visual fields and OCTs at baseline and follow-up. Such an algorithm might then be able to predict from baseline images whether a given patient will be a fast or slow progressor, for example. In one study using 14,034 scans of 816 eyes followed over time and labeled as progression or stable by experts, researchers trained a deep learning model to detect glaucoma progression on SD-OCT. The area under the curve was 0.935, and the researchers reported that the model performed well, closely replicating expert human grading.

“Many glaucoma patients are stable and are followed over time by ophthalmologists, but about five to 10 percent of patients ‘fall off the cliff,’” says Jithin Yohannan, MD, MPH, an assistant professor of ophthalmology at Wilmer Eye Institute, Johns Hopkins University School of Medicine. “Using AI to identify those patients would be incredibly useful, because these are the patients who’d benefit most from closer follow-up and possibly early or more aggressive therapy.”

His group has trained AI models that use a patient’s initial visual field, OCT and clinical information to forecast their risk of rapid worsening or surgery for uncontrolled glaucoma.

“In the future, models such as these might serve as a flagging system of sorts, letting the clinician know they might want to pay extra attention to a particular patient,” he says. “Comprehensive ophthalmologists or optometrists could learn sooner which patients require referral to glaucoma specialists.”

**Tools to detect ongoing worsening.**

Detecting early visual field loss may become easier with AI. One study in 2013 using an artificial neural network to assess visual fields for glaucoma diagnosis reported 93 percent sensitivity, 91 percent specificity and diagnostic performance that was at least as good as clinicians. An unsupervised model for analyzing visual fields was able to identify clinically relevant loss patterns and assign weighted coefficients for each.

Another study of 2,085 eyes’ visual fields used machine-learning analysis to consistently detect progressing eyes earlier than global-, region- and point-wise indices. The time to detect progression in a quarter of the eyes using global mean deviation was 5.2 years; 4.5 years using region-wise; 3.9 years using point-wise and 3.5 years using machine learning analysis. After two additional visits, the time until a quarter of eyes demonstrated subsequently confirmed progression was 6.6 years global-wise, 5.7 years region-wise, 5.6 years point-wise and 5.1 years using machine learning analysis.

Dr. Yohannan’s group has trained models that detect visual field worsening on a series of visual fields over time. Because there’s no gold standard definition of what visual field worsening is, the model his group developed uses a consensus of many previously used algorithms to label the eye as worsening or not worsening.

“When we compared the model to clinicians routinely seeing patients in the office, our model performed better than clinicians in our specific data-
set,” he continues. “Now, our group is using Wilmer patient EHR data, digital field information and optic nerve images to develop AI algorithms that can detect glaucoma worsening more quickly and accurately and then predict which eyes or patients are at high risk for future worsening. Our goal is to follow those eyes or patients more closely, compared to the average patient who walks into the clinic.”

**Identifying patients for clinical trials.** Dr. Yohannan says his group is also working on using AI to improve clinical trials in glaucoma. “Clinical trials, particularly of neuroprotective agents, require large sample sizes,” he explains. “If you’re able to identify eyes that are at high risk for getting worse you can recruit those patients into your clinical trial, and that can actually reduce your sample size requirements. This would make it more cost-effective to do some of these studies.”

Studies reviewing AI in clinical trials have also noted that better patient selection could reduce harmful treatment side effects. Additionally, researchers note that using AI in patient selection could reduce population heterogeneity by harmonizing large amounts of EHR data, selecting patients who are more likely to have a measurable clinical endpoint and identifying those who are more likely to respond to treatment.

This AI-based recruitment would work by analyzing EHRs, doctors’ notes, data from wearable devices and social media accounts to identify subgroups of individuals who meet study inclusion criteria and by helping to spread the word about trials to potential participants. However, this type of implementation still faces data privacy and machine interoperability hurdles. Experts note that final decisions about trial inclusion will still rest with humans.

**Tools to reduce the burden of glaucoma testing.** “Visual field testing is time-consuming and requires significant patient cooperation,” Dr. Yohannan says. “OCT is quicker and more reliable, and if we’re able to detect significant functional worsening (i.e., visual field worsening) using OCT data that could reduce the need for visual field testing. Our group has shown that we can detect VF worsening with OCT data in a subset of patients. This may greatly reduce the need for VF testing in the future.”

**Forecasting from clinical notes.** “My group is very interested in leveraging the richness of the information captured by physicians in free-text clinical progress notes to augment and improve our AI prediction algorithms,” Dr. Wang says. “We adapt natural language processing techniques to work for our specialized ophthalmology language and combine it with other structured clinical information from EHRs to predict glaucoma progression.”

Clinicians wouldn’t use an algorithm blindly … Any recommendations would be taken into consideration by the clinicians when making decisions.

— Felipe Medeiros, MD, PhD

Her group maps words onto numbers so they’re computable by the algorithm. “It’s a technique that takes English language words and turns them into vectors and vector space, so the computer can discern the meaning of the words based on other words close by in the speech or text. We’ve adapted this to work for ophthalmological words. We’re using this to predict whose vision will recover and which patients will need glaucoma surgery in the future.”

**Learning about disease pathogenesis.** Dr. Pasquale is using AI to research primary open-angle glaucoma pathogenesis. He and his colleagues hypothesize that glaucoma is multiple diseases rather than a single disease. “We’re arguing that different patterns of nerve damage, which are reflected by different patterns of visual field loss, might give us clues as to how to better stratify the disease,” he says.

Using new-onset POAG cases in two large-cohort studies, the Nurses’ Health Study and the Health Professionals’ Follow-up Study, he and his colleagues digitized visual fields and used archetype analysis to objectively quantify the different patterns of visual field loss. The algorithm identified 14 different patterns of loss, four of which were advanced-loss patterns.

“It’s interesting to see that a health professional who has access to health care might present with a very significant amount of advanced loss, but this happens frequently in glaucoma because it’s such an insidious-onset disease,” he notes. “While analyzing potential racial predispositions for different field loss patterns, we found that African heritage was an independent risk factor for advanced-loss patterns. Our long-term goal is to identify environmental, genetic, or metabolomic determinants of the disease subtypes.”

**What’s Needed for Clinical Readiness?**

It’s going to take a lot of effort to get AI into the clinical decision-making process. “In the clinic, we collect large amounts of data,” Dr. Pasquale says. “In a single visit, we might get a visual field, an OCT and a fundus photograph, and we just don’t have enough time to digest that data, especially as it accumulates over time for a patient. We’re leaving a lot of information on the table in our decision-making process, and even if we spent hours staring at it, we probably couldn’t wrap our heads around all of it. It’d be great if we had an AI algorithm do that for us. The challenge here would be integrating useful glaucoma AI algorithms into the EHR system.”

Getting an approved algorithm into an EHR in the first place will require working closely with industry, Dr. Yohannan points out. “For instance, our EHR (Epic) doesn’t talk to our im-
aging data management system (Zeiss Forum). We’ll need to come up with an integrated solution so all of these data can be input into the models so the clinician has easy access to an AI risk score.”

It’s a tall order. “It already takes a lot of effort just to make a simple change in an EHR,” Dr. Pasquale says. “Let’s say an approved algorithm is integrated into an EHR system. What will happen is that a fundus photograph or OCT will have to be dipped into a dialog box so it can be analyzed to say whether there’s glaucomatous damage, whether a patient is getting worse, or maybe is a fast progressor. Subjecting clinical data to an AI algorithm takes time and it may hamper clinicians’ ability to see patients. There’s also the feeling among doctors of, ‘I know my patient best and I don’t need a computer to tell me what to do.’ This sentiment, plus the notion that technology is entangling physicians rather than empowering them, is understandable and needs to be addressed as we think about implementing AI into an EHR.”

Next in Line

“In the near future, I think it’s likely we’ll see more algorithms combining multiple sources such as OCTA, visual fields and OCT of the optic nerve or macula along with the whole-patient picture from EHRs, including coexisting diseases and demographics,” he continues. “Algorithms such as these could offer recommendations for how frequently a patient needs to be seen, whether a certain patient will do better with drops compared to laser, or whether a certain patient is more likely to miss drops, for instance.

“Now, clinicians wouldn’t use such an algorithm blindly,” he says. “AI is going to be an instrument to help clinicians make better use of the available diagnostic information and tests. Any recommendations will be taken into consideration by the clinician when making decisions.”

Dr. Yohannan hopes to use raw OCT images to obtain more data.

“Currently we use mostly numeric information that comes from the OCT machine,” he says. “We’re working on extracting raw images, which contain more information than the numbers. The question then is, is there a way we can actually extract better information from those images and give that to the models we’re creating to forecast visual field worsening or detect worsening with even greater power?”

Merging genomic and clinical data may be another future AI development since genomic data can be an independent predictor of glaucoma with a modest level of success. “We’ve found that having a greater genetic burden for the disease increases the risk of needing filtration surgery,” says Dr. Pasquale. “We’ve identified 127 loci for POAG, and we could create a genetic risk score from that data to predict glaucoma with about 75-percent accuracy. That’s all without considering imaging data. Imagine what’s possible if we merge imaging data with genomic data.

“More hospitals are developing biorepositories of high-throughput genetic data,” he adds. “It’s all research right now and not directly connected to EHRs, but perhaps in 10 years when we have acceptance of genomic markers associated with various common complex diseases, it could be merged with imaging data to create more powerful clinical decision-making algorithms.”

“It’s early to say what might actually be deployed and adopted in a widespread fashion,” says Dr. Wang. “As in every field, there is a large chasm between development of an AI algorithm in code, and actually deploying it in the clinic on patients. It may be that some of the first algorithms to be deployed would be glaucoma screening algorithms, or there may be clinical decision support tools to help clinicians predict a glaucoma patient’s clinical trajectory.”

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REVIEW OF OPHTHALMOLOGY WEEKLY NEWS UPDATE:

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A REVIEW OF REFRACTIVE LENS EXCHANGE

Age and refractive error are the main factors when surgeons consider this procedure.

He adds that the quality of vision can be better with RLE than with LASIK, especially for patients with certain types of astigmatism or higher degrees of myopia or hyperopia. “That dictates a large part of the conversation. LASIK is also limited in that it doesn’t treat presbyopia beyond offering monovision in the United States, and so when patients want more than just distance vision, RLE enters the conversation,” Dr. Chu adds.

According to Daniel Durrie, MD, in practice in Overland Park, Kansas, RLE and laser refractive surgery are for different patient populations. “Laser vision correction, whether it’s SMILE, LASIK, or PRK, is really for congenital refractive errors, like myopia, astigmatism, and certain levels of hyperopia that people are born with,” he says. “Surgeons don’t start thinking about RLE until a patient is presbyopic. I think it should be discussed with patients older than 43 because, many times, it takes a couple of years for people to make the decision to have this kind of surgery because they haven’t thought about having their lens replaced, and they didn’t know it was an option.”

Who’s a Good Candidate For RLE?

Dr. Chu notes that prime candidates for refractive lens exchange are those patients who are out of the range of LASIK. “Higher hyperopes are prime candidates because they’re not the greatest LASIK candidates,” he avers. “Additionally, good RLE candidates are typically older than 50 years of age because...
IOLs offer presbyopia correction.”

He’s cautious with lower myopes (~2 D or lower), because these patients already have a good range of near vision, and the lens implant technologies still have the risk of some dysphotopsias and night-vision issues. “In our practice, it’s not an absolute contraindication, but there’s a longer discussion about the potential trade-offs and assessment in patients with low degrees of myopia,” he says.

John Hovanesian, MD, who is in practice in Laguna Hills, California, considers two criteria—age and refractive error—when looking at RLE as an option. “An older patient who is a +3 D or a +4 D is sometimes a better candidate for RLE than for laser refractive surgery,” he says. “Even if the refractive error is within the labeled indication of the laser, the quality of vision with hyperopic LASIK may not be good. Additionally, one might argue that the threshold goes down even below +4 D, especially with older age. As the patient approaches 50, hyperopic laser procedures really are less satisfying. There are exceptions, but most patients have some dysfunctional lens syndrome or early cataract signs that indicate the direction that their vision’s going. Obviously, accommodation is already partially lost by age 50, but lens clarity is beginning to decline as well, and that’s when we start to think about RLE.”

For patients with higher levels of myopia, the decision to pursue RLE has to be balanced against the risk of retinal detachment. “However, most patients who are highly myopic (in the range beyond where LASIK works well) have a posterior vitreous detachment that has previously occurred,” Dr. Hovanesian says, and any patient undergoing lens-based surgery who’s had a previous vitreous detachment is at significantly less risk for retinal detachment. So, although the traditional dogma is that higher myopes have a greater risk of retinal detachment, that’s not always the case if they’ve had a posterior vitreous detachment.”

Dr. Durrie adds that patients who are good candidates for RLE need to have a healthy tear film and no other ocular comorbidities that would prevent them from healing well. This includes significant iritis, corneal guttata or other conditions that would make a surgeon think twice about operating on either the lens or the cornea. “Uncontrolled glaucoma and uncontrolled diabetes are also contraindications to the procedure,” he adds. “Sometimes, we combine MIGS procedures with RLE, but, generally, the patient needs a healthy eye, a healthy tear film, and realistic expectations.”

Dr. Durrie underwent RLE in his nondominant eye 12 years ago to improve his near vision, and he just underwent RLE with a Light-Adjustable Lens on his dominant eye two months ago because he was starting to have decreased distance vision. “I was still 20/20 best-corrected, so I would be considered an RLE, not a cataract,” he says. “I was getting to the point where my quality of vision wasn’t as good, so I just had my lens replaced, and now I don’t need glasses at all. Another benefit is that RLE prevents cataracts, which is a big statement [for a patient]. We can replace your lens, improve your distance and near vision, and prevent cataracts. Many patients don’t realize that once you’ve had your lens replaced, you can’t get a cataract.”

Any premium IOL can be used for refractive lens exchange. Some surgeons who perform premium cataract surgery also perform RLE. “If you’re not doing premium cataract surgery, you’re probably not going to think about replacing somebody’s lens that doesn’t have a cataract yet, so the practice growth usually comes from premium lenses,” says Dr. Durrie. “Or, it can go the other way where you have a refractive surgeon who does corneal refractive surgery, does implantable contact lenses, and then decides to get into refractive lens exchange. I’ve had several practices do that lately, where they either brought in a surgeon to do those lens procedures or refreshed those skills from residency doing lens replacement. But, some purely corneal refractive surgeons that have been building up their practices are now adding RLE.”

ICLs
Dr. Hovanesian notes that laser refractive surgery and RLE aren’t the only options for patients. “The decision between laser refractive surgery and RLE isn’t binary, because there’s an in-between option with the implantable contact lens,” he notes. “Phakic IOLs have been around for decades, but a recent advance with the Staar ICL has made it even more patient-friendly. The EVO model, which has now been...
REFRACTIVE LENS EXCHANGE

approved in the United States, has an opening in the center of the lens, so it’s no longer necessary to perform a peripheral iridotomy. It’s now a one-and-done type of procedure. “Many surgeons are doing these bilateral sequential on the same day,” Dr. Hovanesian continues, “and some are performing them in office-based surgery centers rather than in outpatient ambulatory surgery centers, which means we can reduce some of the costs of anesthesia and facility fees, making it both more affordable and almost as simple as LASIK because it’s bilateral same-day.”

ICLs are only approved in the United States for myopic patients, and they offer the advantage of better-quality vision, especially for higher corrections, users say. “With LASIK, higher corrections have a more significant risk of causing aberrations that degrade the quality of vision,” Dr. Hovanesian adds. “With an ICL, those patients are in the sweet spot of that technology, and they really achieve better uncorrected vision after surgery than their best-corrected vision before surgery. That’s a big statement.”

Pros and Cons of RLE

According to Dr. Chu, the main downside of RLE is matching the right IOL technology to the patient’s needs. With the multitude of intraocular lens choices, including monofocal IOLs, extended depth of focus, light-adjustable and accommodating, as well as multifocal lenses, preoperative education becomes the most critical component for selecting RLE for a specific patient. Understanding patients’ lifestyle needs, including whether or not they tolerate monovision, also helps guide which lens choices are a possibility as well if the patient is a good candidate for refractive lens exchange. “Therefore, it’s not just looking at a patient’s age and degree of refractive error, rather it’s understanding the strengths and weaknesses of each of the available lens technologies and matching it to the specific lifestyle needs and visual demands of each patient,” he says.

As IOL options have improved and surgery has become safer, this has allowed more patients to become candidates for lens replacement surgery at younger ages and at earlier stages in their dysfunctional lens syndrome journey. “Because of this, training the clinic staff and keeping up with the advances in the technologies has been the most challenging part in a surgical practice,” Dr. Chu adds.

With the multitude of intraocular lens choices, including monofocal IOLs, extended-depth-of-focus, light-adjustable, accommodating, as well as multifocal lenses, preoperative education becomes the most critical component for selecting RLE for a specific patient.

Another downside is that it’s more invasive than laser refractive surgery, and most surgeons operate on one eye at a time. “It has all of the potential complications of an intraocular procedure, such as retinal detachment and endophthalmitis, which isn’t a meaningful risk with PRK and LASIK,” Dr. Hovanesian adds.

While it does have some downsides, it also has some significant benefits, proponents say. One advantage is that it’s the last eye procedure most patients will ever need. “It’s highly accurate, it obviates the future need for cataract surgery, and it can give the patient multifocality or a range of vision that LASIK can’t,” Dr. Hovanesian says. “LASIK is a depreciating asset for the patient. As the lens becomes more mature, the quality of vision changes, the refraction may shift, and the patient may lose accommodation. Whereas, with a lens-based procedure like RLE, the quality of vision typically improves immediately and stays that good for life. Patients don’t have to undergo future surgery, and most patients are very pleased with the range of uncorrected vision that they can achieve.”

According to Dr. Chu, an advantage of RLE is that a lens implant can be removed and exchanged if the patient is unable to adapt to unwanted visual side effects. The typical scenario involves exchange of a multifocal lens for a monofocal lens due to intolerance to dysphotopsia. A light-adjustable lens can also be considered as a replacement lens in this situation. “Exchanges are more straightforward when performed before YAG capsulotomy, but can also be done post-YAG capsulotomy,” he explains.

The Future

Dr. Chu notes that lens implants have been around since 1949. “Patients always ask about switching out their current lens if something better comes along in the future,” he says. “Right now, my answer is still most likely not. After a certain amount of time, it becomes more difficult to remove the lens, and most of the new lens technologies require a pristine capsular bag for stability and good outcomes. We tell patients that we usually have one chance to put in the best lens for your eye. Early on, lenses can be exchanged, but down the road, don’t expect that the lens implant can be swapped out like snow tires.”

Going forward, RLE may continue to grow in popularity. “More people are becoming interested in refractive lens exchange because it’s a presbyopic solution,” says Dr. Durrie. “Presbyopia is a lens disease, not a corneal disease, so it should be treated with a lens exchange.”
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Sincerely,

Kuldev Singh, MD, MPH

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Kuldev Singh, MD, MPH

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Do you know the latest information on medications with ocular side effects recently approved by the Food and Drug Administration for use in children? These drugs can cause everything from blurred vision and photophobia to cataracts, so it pays to be aware of their safety profiles. Here, we’ll provide insights on these therapeutics and the associated ocular complications to be on the lookout for in your pediatric patient population.

The Medications
The table on the following page summarizes the recently approved medications and a few other commonly used pediatric medications with ocular toxicities. Following are the medications and their toxicity issues to be aware of.

• Cystic fibrosis medications
  Elexacaftor/Ivacaftor/Tezacaftor (Trikafta), Ivacaftor/tezacaftor (Symdeco), and Ivacaftor/lumacaftor (Orkambi) are combination drugs in which multiple CFTR potentiators are formulated into a single agent to increase efficacy. The FDA approved ivacaftor for patients with CF 4 months of age and older with at least one responsive mutation in the cystic fibrosis gene. The FDA has also approved combination CFTR potentiator drugs, including ivacaftor/lumacaftor for children 2 years of age and older and elexacaftor/ivacaftor/tezacaftor and ivacaftor/tezacaftor for children 6 years of age and older.

—Ocular side effects. Investigators have reported non-congenital cataracts (cortical and subcapsular) by specific gene mutations. Elexacaftor/ivacaftor/tezacaftor (Trikafta), ivacaftor/tezacaftor (Symdeco), and ivacaftor/lumacaftor (Orkambi) are combination drugs in which multiple CFTR potentiators are formulated into a single agent to increase efficacy. The FDA approved ivacaftor for patients with CF 4 months of age and older with at least one responsive mutation in the cystic fibrosis gene. The FDA has also approved combination CFTR potentiator drugs, including ivacaftor/lumacaftor for children 2 years of age and older and elexacaftor/ivacaftor/tezacaftor and ivacaftor/tezacaftor for children 6 years of age and older.

Figure 1. Wide-field photographs (Optos) showing panuveitis seen in a 40-year-old patient with cancer drug-induced uveitis (nivolumab). Fluorescence angiography showed late peripheral and macular leakage.
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surgery. Ophthalmologic evaluation for children on cystic fibrosis medications should include age-appropriate visual acuity testing, biomicroscopy (standard or portable slit lamp), and full retinal examination. Cataracts that are less than 3 mm in diameter or of partial density may be observed. In older children, ophthalmologists should consider cataract surgery for any opacity causing a decrease in quality of life. After cataract surgery, ophthalmologists should initiate optical rehabilitation and amblyopia management.

* Selumetinib (Koselugo) for neurofibromas and optic pathway gliomas. Selumetinib is a drug that blocks the mitogen activator protein kinase (MAPK) pathway. Specifically, it inhibits mitogen-activated protein kinase enzymes (MEK), causing cell death and stopping tumor growth. Oncologists have used MEK inhibitors to treat metastatic melanoma and other cancers in adults. In 2020, selumetinib received FDA approval for the treatment of symptomatic, inoperable plexiform neurofibromas in patients with neurofibromatosis (NF) type 1 who are 2 years and older. Selumetinib also shows promise in treating pediatric patients with non-NF type 1 associated optic pathway gliomas, though it’s not approved by the FDA for this indication.

**Ocular complications.** Patients treated with selumetinib have reported visual changes, including blurred vision and photophobia, and have developed cataracts and ocular hypertension. In adult patients treated with MEK inhibitors, the severe ocular complications of retinal pigment epithelial detachment and retinal vein occlusion have been noted. Pediatric patients have also shown outer retinal separation. The RPE detachment associated with selumetinib is typically bilateral and symmetric. The patient’s symptoms can vary from nothing at all to blurred vision, altered color perception, shadows, light sensitivity, metamorphopsia and glare. Diagnosis of RPE detachment may require macular OCT. Separation occurs because of RPE degeneration secondary to MEK pathway inhibition. Under normal conditions, activation of the MEK pathway supports the RPE. The RPE detachment associated with selumetinib typically doesn’t result in irreversible loss of vision or eye damage and resolves with discontinuation of the medication.

Uveitis is another severe but rare ocular complication associated with MEK/BRAF inhibitor and other cancer drug treatments such as immune checkpoint inhibitors in adult patients. MEK/BRAF inhibitor-related uveitis causes severe uveal tract inflammation that may lead to irreversible vision loss. Figure 1 shows an example of cancer-drug-induced uveitis. The fundus photographs are from a 40-year-old adult patient with cancer-drug-induced uveitis due to treatment with nivolumab, an immune checkpoint inhibitor. Because uveitis is such a rare occurrence, it remains to be determined if there’s an association between uveitis and MEK inhibitors in the pediatric population. However, pediatric ophthalmologists should consider using extra vigilance in looking for signs or symptoms of uveitis in their patients being treated with selumetinib.

**— Monitoring.** The prescribing information recommends baseline ophthalmic assessments in pediatric patients starting selumetinib. The package insert also suggests ophthalmic exams at regular intervals during treatment and for any new or worsening visual changes. In patients with visual changes, ophthalmologic evaluations should include a best corrected visual acuity, intraocular pressure, and slit lamp fundoscopy. Physicians should also consider a macular OCT.

Ophthalmologists need more information to determine how often these ocular side effects occur in the pediatric population. There are no published screening protocols. For younger patients, detecting RPE detachment without macular OCT may prove challenging for pediatric ophthalmologists.

Currently, the main management options are cataract surgery and withholding or discontinuing the medication. The drug’s package insert suggests permanently

<table>
<thead>
<tr>
<th>Ocular Side Effect(s) FDA Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accommodative insufficiency, retinopathy, and corneal edema deposits</td>
</tr>
</tbody>
</table>

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**OCULAR SIDE EFFECTS OF NEW FDA-APPROVED, COMMONLY USED PEDIATRIC MEDICATIONS**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name(s)</th>
<th>Indication(s) for Pediatric Patients</th>
<th>Ocular Side Effect(s)</th>
<th>FDA Drug Information Hyperlink</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixacaftor</td>
<td>ivacaftor, trikaf, symdeco, and kalydeco</td>
<td>cystic fibrosis</td>
<td>cataract</td>
<td><a href="https://tinyurl.com/2p8dj6fs">https://tinyurl.com/2p8dj6fs</a></td>
</tr>
<tr>
<td>Koselugo</td>
<td>selumetinib</td>
<td>plexiform neurofibroma, optic pathway glioma</td>
<td>cataract, ocular hypertension, RPE detachment, and retinal vein occlusion</td>
<td><a href="https://tinyurl.com/3kx5z9up">https://tinyurl.com/3kx5z9up</a></td>
</tr>
<tr>
<td>Dupixent</td>
<td>dupilumab</td>
<td>atopic pathway glioma</td>
<td>conjunctivitis, cicatricial ectropion, dry-eye syndrome, and limbal stem cell deficiency</td>
<td><a href="https://tinyurl.com/2apthjnk">https://tinyurl.com/2apthjnk</a></td>
</tr>
<tr>
<td>Sabril</td>
<td>vigabatrin</td>
<td>infantile spasms, refractory partial complex seizures</td>
<td>permanent concentric visual-field constriction</td>
<td><a href="https://tinyurl.com/577kwug">https://tinyurl.com/577kwug</a></td>
</tr>
<tr>
<td>Topamax</td>
<td>topiramate</td>
<td>epilepsy, migraine prophylaxis</td>
<td>acute myopia, secondary angle-closure glaucoma, and visual field defects</td>
<td><a href="https://tinyurl.com/2cu7nzhz">https://tinyurl.com/2cu7nzhz</a></td>
</tr>
<tr>
<td>Plaquenil</td>
<td>hydroxychloroquine</td>
<td>malaria, lupus, and rheumatoid arthritis</td>
<td>accommodative insufficiency, retinopathy, and corneal edema deposits</td>
<td><a href="https://tinyurl.com/55x2tja">https://tinyurl.com/55x2tja</a></td>
</tr>
</tbody>
</table>

*Not FDA-approved for use in pediatric patients*
discontinuing selumetinib for retinal vein occlusion and, in cases of RPE detachment, withholding selumetinib while checking optical coherence tomography assessments every three weeks until resolution and then resuming at a reduced dose. As uveitis is a rare complication, currently there are no guidelines for its management in these patients. Collaborative care nuanced to the disease specific to the patient is advised.

• **Dupilumab (Dupixent).** Dupilumab is an interleukin (IL)-4 receptor inhibitor administered by subcutaneous injection. It was recently FDA-approved for “the treatment of moderate to severe atopic dermatitis in pediatric patients aged six months to 5 years whose disease is not adequately controlled with topical therapies or when those therapies are not advisable.” Dupixent has already been approved for the treatment of the following indications:
  - moderate to severe atopic dermatitis in patients six years of age and older;
  - maintenance treatment of severe asthma in patients 12 years of age and older; and
  - the treatment of eosinophilic esophagitis in patients 12 years of age and older weighing at least 40 kg.

  — **Ocular complications.** A commonly reported ocular side effect noted in children and adults is conjunctivitis. In the adult literature, there have also been cases of symblepharon and cicatricial ectropion, dry-eye syndrome, and limbal stem cell deficiency. Researchers hypothesize that dupilumab-associated conjunctivitis might be due to goblet cell loss, heightened OX40 ligand activity, eosinophilia and increased Demodex infestation due to changes in the ocular surface environment. In the case of the limbal stem cell deficiency, the report speculated that it occurred because of continued use of the medication well after the appearance of symptoms.

  Figure 2 shows conjunctivitis and symblepharon developed in an adult patient treated with dupilumab. In this patient, both conjunctivitis and symblepharon improved but didn’t completely resolve with treatment. In terms of monitoring recommendations, that’s still an open question. The need for and frequency of screening exams in the pediatric population require further investigation.

  — **Management of complications.**

Management consists of topical steroids and/or topical immunomodulators such as tacrolimus or cyclosporin, as well as discontinuing dupilumab in rare cases. Artificial tears and topical anti-histamines aren’t effective. Effective treatment stops the inflammatory process. It’s thought that topical steroids and/or topical immunomodulators prevent epithelial cell death by increasing goblet cells.

In conclusion, new FDA-approved medications have significant benefits for pediatric patients with a variety of diseases. However, ophthalmologists must be aware of potential ocular complications, and develop proper screening and treatment protocols when necessary to preserve vision in our patients. In addition, it is vital to keep an open line of communication with the managing specialist(s) of patients with these disorders to optimize care.
Samantha Orr, MD, BMSc
Austin Pereira, MD, MEng
Netan Choudhry, MD, FRSC, FASRS
Toronto

Since its inception in the 1990s, optical coherence tomography has become a crucial tool in the practice of ophthalmology by informing diagnosis, disease monitoring and long-term prognosis. The ability of this technology to capture the peripheral retina has allowed for new and expanded clinical applications. In the course of its use and development, OCT technology has spawned widefield and ultra-widefield imaging methods that allow fields of view of up to 220 degrees. With the advent of these UWF imaging modalities, many researchers have initiated studies investigating the utility of UWF-OCT imaging. In this literature review, we’ll outline four disease entities in which UWF-OCT has shown promise: retinal detachments; pathological myopia; peripheral retinal degenerations; and choroidal pathologies, as well as highlight the uses of this modality in pediatrics and UWF-OCT angiography.

**WF and UWF Defined**
In 2019, the International Widefield Imaging Study Group defined widefield imaging as a field of view of approximately 60 to 100 degrees, capturing the mid-periphery of the retina up to the posterior edge of the vortex vein ampulla.1 It defined ultra-widefield imaging as an image of the far periphery of the retina, including the anterior edge of the vortex vein ampulla and beyond.1 This represents a 110 to 220-degree field of view. A depiction of these definitions appears in Figure 1.

Until recently, capturing the far periphery of the retina with OCT was nearly impossible. However, the Heidelberg Spectralis HRA-OCT (Heidelberg Engineering USA) (using a steering technique), the Silverstone (Optos PLC Edinburgh), the Plex Elite 9000 (Zeiss, Oberkochen, Germany) and the Xephilio OCT-S1 (Canon Medical Systems, Japan) have introduced UWF capabilities. A company called Toward Pi has also developed a swept-source OCT machine with an 81 x 68 degree field of view and an A-scan speed of 400 kHz.2

As mentioned, in the following sections we’ll look at the utility of WF and UWF in various conditions.

**Retinal Detachment**
There’s potential for the use of UWF-OCT in the diagnosis, monitoring, and management of retinal detachments. Microstructural retinal details such as photoreceptor integrity and resolution of subretinal fluid are difficult to ascertain on clinical exam or UWF fundus photography. UWF-OCT, however, acquires crucial information both before and after retinal detachment treatment. Toronto’s Wei Wei Lee, MD, and colleagues presented longitudinal findings captured by the Optos Silverstone that provided insight into the response of the retina to treatments including laser retinopexy and cryopexy.3 OCT findings post-cryopexy revealed separation of the choroid and sclera in the first week, a previously undescribed finding. Other OCT findings confirmed what’s been described in past histological analyses, including coagulative necrosis and retinal splitting after laser retinopexy, as well as retinal layer destruction and RPE

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Dr. Regillo is the director of the Retina Service of Wills Eye Hospital, a professor of ophthalmology at Thomas Jefferson University School of Medicine and the principle investigator for numerous major international clinical trials.

Dr. Yonekawa is an assistant professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University. He serves on the Education Committee of the American Society of Retina Specialists and on the Executive Committee for the Vit Buckle Society, where he is also the vice president for academic programming.
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Rick Bay served as the publisher of The Review Group for more than 20 years. To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty. To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

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separation post-cryopexy. A post-hoc analysis of the PIVOT trial comparing vitrectomy and pneumatic retinopexy for the treatment of retinal detachment examined postoperative outer retinal folds on OCT. They found that these ORF were associated with poorer visual outcomes at one year, and that those treated with vitrectomy were at greater risk of postoperative ORF. Although they evaluated OCT of only the posterior pole, these findings suggest that UWF-OCT in these patients would provide additional information about retinal healing after retinal detachment repair in the mid-far periphery where retinal breaks typically occur.

UWF-OCT can also aid in the differentiation of retinal detachments from degenerative retinoschisis or schisis detachments in cases where the clinical findings may be ambiguous (Figure 2). Cases clinically diagnosed as retinoschisis have been shown to have retinal detachment on OCT and vice versa. In 2014, Marilene Stelhouwer and her colleagues at the Academic Medical Centre at the University of Amsterdam found that out of 18 presumed retinoschisis cases, three were shown to have retinal detachment on peripheral OCT, while another study reported a rate of six out of 53 eyes. This distinction is particularly relevant as the management for these two conditions differs significantly, with retinoschisis often being a benign condition requiring no intervention. However, one indication for intervention in retinoschisis is retinal holes, a finding which can also be captured on peripheral OCT. These preliminary studies show that UWF-OCT may be able to yield more useful information in the diagnosis and management of retinal detachment.

**Pathologic Myopia**

Since its development, UWF-OCT has been used to investigate and characterize features of high myopia, including posterior staphylomas, dome-shaped macula (DSM), and choroidal thickness, providing insight into classification and pathophysiology of these findings. Although DSM was originally considered a type of staphyloma, UWF-OCT has demonstrated that it’s distinct in its pathophysiology. DSM has been defined as an inward bulging of at least 50 µm involving the retinal pigment epithelium and Bruch’s membrane (Figure 3). Findings on UWF-OCT now suggest that DSM is related to an abnormal posterior scleral curvature.

With regards to classification of staphylomas, UWF-OCT can aid in distinguishing wide and narrow varieties and allows for quantitative measurement of these staphylomas. In eyes with narrow staphylomas, Tokyo’s Noriko Nakao, MD, and her colleagues found that higher axial lengths were correlated with more abrupt staphyloma edges. This wasn’t the case with wide staphylomas, further differentiating these staphyloma categories. In another study, Tokyo’s Kosei Shinohara, MD, and co-workers reported that UWF-OCT may be more sensitive than 3D MRI in the detection of staphylomas, although the results weren’t statistically significant. Detection and monitoring of these staphylomas provide information about progression and risk of complications.

**Peripheral Retinal Degeneration**

Peripheral retinal degenerations are pathologies that may demonstrate the highest utility for UWF-OCT to date. UWF-OCT can provide clear characterization and documentation of these peripheral pathologies including lattice degeneration, retinal tufts, retinal tears, retinal holes and paving-stone degeneration. The feasibility of acquiring clinically useful OCT of these pathologies in practice has been demonstrated in several studies. In 2016, one of this article’s authors, Dr. Choudhry, used a steering technique to acquire UWF spectral-domain OCT of the peripheral retina and described structural features of these peripheral pathologies. In 2021, Simrat K. Sodhi and her co-authors at Vitreous Retina Macula Specialists of Toronto demonstrated that high quality and clinically valuable SS-OCT of the mid and far periphery could be captured without montage or steering. That same year, New York’s Kyle Kovacs, MD, and colleagues reported that the use of UWF-OCT provided meaningful clinical information to inform management in 38 percent of eyes imaged. This year, Paulo Stanga, MD, and co-workers (one of whom is an employee of OCT-maker Canon Medical Systems) used a novel UWF-OCT device in a retrospective study to image pathology of the peripheral retina and were able to correlate findings with histological photomicrographs showing the retina and vitreous attachments. The researchers found that, in addition to microstructural details in the peripheral retina, OCT can also provide important information about the vitreoretinal interface and the presence or absence of traction. Such distinctions in pathology and associated features can help avoid invasive management by ruling out tears and holes in cases of vitreoretinal tufts or by ruling out vitreoretinal traction in cases of lattice degeneration.

**Choroidal Pathology**

Choroidal pathologies are entities that can present in the peripheral retina where clinical exam alone may not be sufficient to make a diagnosis. UWF-OCT has been used to differentiate and diagnose choroidal melanoma and choroidal nevi in the retinal periphery. Important risk factors for transformation of nevi into melanoma include presence of subretinal fluid on OCT. In the case of peripheral lesions, UWF-OCT allows the detection of subretinal fluid and estimation of lesion size. Peripheral exudative hemorrhagic chorioretinopathy (PEHCR) lesions have been found to simulate the appearance of choroidal melanoma and are thus important to properly characterize. Since PEHCR lesions are usually located in the reti-
nal periphery (89 percent between the equator and ora serrata), use of UWF or peripheral OCT is particularly valuable. The presence of retinal exudation and RPE atrophy can assist in differentiating PEHCR from choroidal melanoma. In a retrospective study of PEHCR lesions in 50 eyes of 35 patients, detection of subretinal fluid on OCT was a risk factor for future macular involvement, intraocular bleed and loss of vision.19 Lesion extension beyond three clock hours also denoted high-risk eyes.19 Subgroup analysis from this study suggested that treatment of these high-risk eyes may protect against macular involvement.19 Continued research using peripheral OCT could further inform treatment recommendations.

Shanghai’s Yi Xuan, MD, and colleagues examined a series of choroidal osteomas using Toward Pi’s novel SS-OCT and OCTA technology, allowing an ultra-high resolution 120-degree field of view, capturing the entire tumor. This imaging modality was capable of detecting choroidal neovascularization, which can be difficult on traditional imaging modalities due to the dense nature of the mass and RPE changes.2

UWF-OCT in Pediatrics

Ophthalmic imaging in pediatric patients presents a unique challenge with regard to positioning and fixation. As in adults, subtle anatomic changes detectable with OCT imaging are clinically valuable in many conditions. One solution to address challenges with positioning is the use of handheld OCT devices. Thanh-Tin P Nguyen, MD, of Oregon’s Casey Eye Institute, and colleagues have shown the utility of a handheld SS-OCT device in non-sedated pediatric patients in the neonatal ICU, and in sedated patients in the operating room.20,21 Their widefield prototype device has a 105-degree field of view with the option of displaying real-time en-face OCT images.20,21

Particularly for pediatric conditions such as retinopathy of prematurity, this technology can play a role in screening and monitoring, and could even provide new pathophysiologic insights.20 With widefield OCT, the physician can determine the area of vascularized retina and the vascular/avascular border.20 The user can accurately detect and characterize neovascularization, particularly extraretinal neovascularization, which is important to the classification of ROP.20 Other clinically valuable OCT findings include changes in the vitreoretinal interface, which might inform management decisions in several pathologies. In pediatric retinal detachments, OCT findings can distinguish between tractional and exudative detachments.21 Objective OCT measures can also help monitor changes over time.

Furthermore, widefield OCT can be valuable in cases of retinoblastoma, as tumors and subclinical-sized tumors can be detected in the retinal periphery.21,22 The utility of OCT in the detection of subclinical retinoblastoma tumors less than 400 µm, undetectable by ophthalmoscopy, has been well-established.22-24 Marie-Claire Gaillard, MD, and colleagues from the University of Lausanne in Switzerland, presented a case series of 16 subclinical recurrent tumors detected with a commercial handheld OCT device.21 Although this device didn’t have widefield capabilities, it demonstrated the benefit of OCT in the monitoring of patients with retinoblastoma. This may help detect recurrences earlier, which could have a significant impact on survival and visual outcomes. However, it can also provide important clinical details about the tumor, which may inform management decisions.

The further evolution of pediatric widefield OCTA could prove valuable in the detection and management of intraocular tumors.

UWF-OCT Angiography

OCT’s evolution has led to the development of non-contrast angiography capabilities. Though it’s currently not widely used, OCTA can be valuable as a non-invasive, safe and easily repeatable alternative to dye-based angiography with fluorescein or indocyanine green.25 An advantage of OCTA is the ability to create high-resolution, depth-resolved angiographic images, which can be correlated with flow overlay B scans. A major limitation of early OCTA technology was the limited field of view, but newer technology has allowed for wider field OCTA.26 Similar to OCT imaging standards, the International Widefield Imaging Study Group in 2019 recommended OCTA definitions for widefield and ultra-widefield. Widefield OCTA must capture all four quadrants of the retina including the posterior edge of the vortex veins, while ultra-widefield OCTA requires imaging beyond the anterior edge of the vortex veins. If
not all four quadrants are captured, it must be labeled as asymmetric widefield, or asymmetric ultra-widefield, OCTA.¹

One area in which widefield OCTA can be useful is in the evaluation of diabetic retinopathy. OCTA of the peripheral retina in DR can outline areas of non-perfusion and document vascular changes such as vessel pruning or neovascularization. The additional information afforded by OCTA may improve classification of diabetes severity. For example, in a retrospective, cross-sectional study, Fupeng Wang, PhD, of the University of Washington-Seattle, and co-workers used widefield OCTA to look at the ratio of nonperfusion (RNP) in eyes with diabetes without retinopathy, eyes with non-proliferative DR and eyes with proliferative DR.²⁷ The RNP was significantly different between these groups. Interestingly, subgroup analysis suggested that nonperfusion in the peripheral retina (between 50 to 100-degree field of view) was the most valuable in grading DR severity.²⁷

Differentiation of intraretinal microvascular abnormalities from neovascularization is also key in classifying DR severity. IRMA can be distinguished on widefield OCTA by the presence of intraretinal collateral vessels, with no flow signals above the internal limiting membrane.²⁸ Presence of IRMA denotes severe NPDR and represents a high risk of progression to PDR.²⁹ Although fluorescein angiography is considered the gold standard for detection of retinal neovascularization, two studies, one a cross-sectional study in 82 eyes by Francesco Pichi, MD, of the Cleveland Clinic Abu Dhabi and co-authors and a retrospective study in 82 eyes by Moorfields’ Hagar Khalid, MD, and co-authors, showed that the detection rate of NV on widefield OCTA may be better than detection on FA, color photography and clinical examination.³⁰,³¹

Research has found clinical value in widefield OCTA assessment of retinal vein occlusions. In two studies (consisting of 43 patients and 26 patients, respectively), detection and quantification of areas of retinal non-perfusion with OCTA appears to correlate closely with FA.³²,³³ Since the peripheral retina often has larger areas of nonperfusion, widefield OCTA may allow a more accurate estimation of the extent of nonperfusion.³⁴ In the first study, Agnès Glacet-Bernard, MD, and her colleagues at Paris-Est Créteil University in France, found that using a 60-degree field of view rather than a 12x12 40-degree field of view revealed nonperfusion in 30 percent more eyes.³⁰ In a different study, Moorfields’ Josef Huemer, MD, and his co-authors used OCTA to describe different patterns of neovascularization in RVO: a sea-fan type and a nodular type.³² They noted a tendency for nodular neovascularization to be misdiagnosed as retinal hemorrhage on clinical exam, highlighting the clinical contribution of OCTA in these patients.³²

In a retrospective study of 54 patients, Shanghai’s Wenyi Tang, MD, and colleagues found that the depth-resolved nature of OCTA allowed for evaluation of the pericentral capillary-free zone (paCFZ), which is the avascular area surrounding retinal arteries, measured in the superficial capillary plexus.³³ This has been investigated as a potential biomarker in RVO, and has been shown to be larger in eyes with branch RVO.³³ The researchers looked at this measure before and after anti-VEGF therapy and found an improvement in paCFZ with treatment.³³ Dr. Tang’s group also found that lower ratio of paCFZ to artery area tend to predict better visual outcomes at 12 months with anti-VEGF injections.³³

In conclusion, though it’s not currently widely used, UWF-OCT can be valuable in detection of pathology, such as subclinical retinoblastoma and diagnosis of clinically uncertain presentations, such as retinoschisis. It can play a role in monitoring of disease progression, such as myopic staphylomas, and inform treatment decisions through clear information about structural anatomy such as the vitreoretinal interface.

Despite significant improvements in technology, there exists many limitations to its application in practice. One obvious limitation
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Best regards,
Derek DelMonte, MD, Kourtney Houser, MD, and Jonathan Rubenstein, MD

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is the cost of machines with wide-field or ultra-wide-field capabilities. Given the financial outlay required, consideration must be given as to the clinical utility of OCT and OCTA, as well as the other capabilities of these machines. For example, some devices offer ultra-wide-field OCT capability, but can also be used to capture ultra-wide-field pseudocolor photography, autofluorescence imaging, and fluorescein and indocyanine green angiography. Each clinician must evaluate the utility of these modalities in their practice. Another factor to consider is the challenge in image acquisition. Many artifacts must be managed with wide-field imaging, such as eyelid artifact, inversion artifact and motion artifacts.

The majority of the scans also depend on the patient’s ability to fixate for longer periods of time, particularly with OCTA, as more information is being acquired. As machines evolve, the speed of acquisition increases, making this technology more useful in the ophthalmic population. Many commercial devices have an acquisition speed of 100 kHz (or greater), including the Optos Silverstone, the Plex Elite 9000, and the Xephilio OCT-S1 but the newer T oward Pi clecular swept-source OCT.  


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Surgical Video by: Richard J. Mackool, MD

**Video Overview:**

Intravitreal dislocation of a posterior chamber IOL has occurred in the only sighted eye of a 92 year old patient with advanced corneal endothelial cell loss. A moderately large Soemmering's ring is present, and the issue that this presents is discussed.

**Learning Objective**

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

- employ surgical options in eyes with posterior chamber IOL dislocation.

To view CME video go to: www.MackoolOnlineCME.com

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.
Should You Stop Driver’s License Renewal?

Even mild visual field loss can have serious on-road consequences. Here’s guidance.

Jonathan S. Myers, MD
Philadelphia

Accidents happen, but they may be happening more among glaucoma patients. Most glaucoma patients don’t notice their gradual peripheral field loss and continue to drive since they retain good central vision. However, we see in the literature that even small amounts of peripheral field loss can hinder safe driving. Do you and your patients know their driving risk and whether they meet their state’s vision requirements for driving?

At the same time, there are plenty of other factors that might make someone unsafe to drive that have nothing to do with their vision, some of which ophthalmologists don’t typically assess. Cognitive issues, processing speed, executive function, planning ability, reaction time, coordination and cellphone use may all come into play. Other drivers also pose a potential threat. So, when and how should you tell a patient to hang up the keys?

Here, I’ll review visual requirements for driving, what we know about glaucoma patients’ on-road performance and discuss how I approach the inevitably difficult conversation with the patient.

State Driving Regulations

Vision requirements for driving vary considerably across the United States, so it’s helpful for ophthalmologists to know their state’s regulations. Many states set minimum visual acuity at 20/40, which is also how low-vision is defined by the National Institutes of Health. Other states require at least 20/100 visual acuity for some driving, which falls within the World Health Organization’s low-vision definition of visual acuity between 20/60 and 20/200.

Most requirements specify whether the visual acuity listed is for one or both eyes and/or include certain restrictions for poorer vision such as daytime-only driving or avoiding freeways.

Visual field requirements for driving in the United States may range anywhere from 55 to 150 degrees. Some states don’t have minimum visual field requirements or require vision testing for license renewal. As a quick reference, you can find a table of vision restrictions for non-commercial licensure at eyewiki.aao.org/Driving_Restrictions_per_State. As you might surmise, vision requirements for commercial licensure are much stricter.

Most of these vision requirements for driving weren’t written by ophthalmologists. Perhaps that’s a good thing given our limited experience writing legislation, but on the flip side, many of the state regulations fail to specify important details. What does it mean to say that Tennessee drivers, for example, are required to have a “visual field diameter of no less than one hundred fifty (150) degrees without the use of field expanders…”? Is that 150 degrees continuous? Is that 150 degrees in which you can make out a large object, or 150 degrees in which you can make out a small stimulus? Additionally, most states don’t specify the vertical component, just the left-right horizontal component. Is driving with a complete altitudinal defect acceptable?

The state requirements are also often silent on the question of how we establish the field of vision. They don’t specify the stimulus size or defect depth. There are customary ways that people perform the testing, but the type of test isn’t usually specified in the requirements. One customary way is to use the Goldmann kinetic perimetry stimulus III-4e as a criterion, but few of us are routinely using Goldmann perimetry. On the other hand, static perimetry such as the Humphrey Visual Field Analyzer is widespread. A 10-decibel stimulus on the Humphrey would be somewhat analogous to missing the Goldmann III-4e—that’s about a 20-dB defect in the central field. So, it’s a fairly decent-sized defect that counts for the purposes of driving. It’s not just a mild depression but a pretty solid loss at one or several points in that area.

Field Loss & Car Accidents

Though the absolute risk of having...
an accident in a given year is fairly small for most drivers, real-world data shows that this risk is greater among glaucoma patients. Cynthia Owsley, MD, and colleagues have been researching the impacts of aging on vision for a number of years. One of the groups’ studies investigated motor vehicle collision risk among 2,000 licensed drivers in Alabama, aged ≥70 years. They found that glaucoma patients (n=206) had more actual collisions (1.65 times higher MVC rate [95% CI, 1.2 to 2.28; p=0.002]) and that patients with impaired left visual fields were more likely to have been involved in an accident (risk ratio: 3.16; p=0.001; mean sensitivity <22 dB).

A study by Balwantray Chauhan, PhD, and colleagues examined on-road driving performance among glaucoma patients (n=20; better-eye MD -1.7 dB; worse-eye MD -6.5 dB; all ≥20/40, ≥120 degrees VF) vs. controls (n=20). All of these glaucoma patients would generally be considered legal to drive based on their visual field loss—they all have reasonably good central and peripheral vision. The better eyes had very mild defects and the worse eyes had moderate defects, on average. Even though they meet the legal requirements for driving and had one eye that was very good, these glaucoma patients were still three times more likely to have incidents requiring intervention by the person riding alongside (a professional driving instructor) in this on-road test. After adjusting for age, sex, medications and driving exposure, the glaucoma patients were up to six times more likely to require intervention. In self-reported driving assessments, most patients considered their own driving to be relatively good.

The authors hinted that there may be additional issues besides vision at play. Glaucoma is more common as we age, so some of these concurrent issues such as cognition speed and processing may make driving more challenging or less safe. In fact, a driving simulation study published in *BMC Ophthalmology* in 2020 reported that glaucomatous visual fields and neurocognitive function are independently associated with poor lane maintenance. In simulator studies, glaucoma patients are also more likely to have accidents. A study in Japan noted that though the severe glaucoma patient participants (n=95) had good central vision (20/25 in the better eye), the better eye had a lot of field loss (MD -18 dB). Collision involvement was significantly associated with decreased inferior visual field mean sensitivity in the mid periphery from 13 to 24 degrees (p=0.041), older age and lower visual acuity (p=0.018 and p=0.001).

As part of a study we presented as a poster at the 2019 ARVO Meeting in Vancouver testing glaucoma patients’ performance on real-world tasks such as identifying misspelled words and matching pairs of socks, we also asked patients if they’d been involved in any accidents in the past five years. Indeed, the glaucoma patients were about twice as likely to be involved in self-reported motor vehicle collisions than average for similarly aged healthy drivers. Overall, we find in the literature that field loss is linked to accidents, particularly inferior and left visual field loss. This makes sense as most of the threats on the road come from the left in our country. The car that’s going to hit you first at an

Patient 1 has a fairly typical glaucoma field. Much of the field loss in one eye is reinforced by areas of seeing in the other. The field loss in these two eyes doesn’t overlap in space.
intersection comes from the left side. Can your patient see someone who runs a stop sign?

**Detecting A Problem**

Considering the literature, how comfortable would you be telling the following patients whether or not they can drive?

**Patient 1** (see image, page 73) has a fairly typical glaucoma field, mainly superonasal steps with moderate superior arcuates that are primarily nasal. In this case, much of the patient’s field loss in one eye is reinforced by areas of vision in the other eye, so the field loss in these two eyes isn’t overlapping in space. This is a patient who may well be okay to drive. I’d counsel this patient about the increased risk of accidents, but I’d also tell them that in most states, they meet the legal requirements to drive if they don’t have other comorbidities.

**Patient 2** (image above) has complete left-sided field loss in both eyes, such as from a stroke. In many areas there are organizations that offer driver therapy or occupational therapy, including formal driving testing and rehabilitation programs. Internet searches turned up many of these programs. I think it’s great to refer patients like this case example who may be able to drive safely with some professional help.

**Patient 3** (see image, facing page) has more advanced glaucoma fields with a central island of vision in the left eye and a fairly dense arcuate in the right eye that approaches central fixation. This patient has several of the risk factors, including overall field loss, that the previously mentioned studies suggest puts them at greater risk for accidents. This patient’s field loss overlaps leftward and downward. Whether they meet the legal requirements in their state or not—I’m not sure I’m comfortable saying that this patient will be okay to drive.

State restrictions usually specify that the patient meet requirements in the horizontal meridian. This patient’s defect goes right up to the meridian, but we don’t generally test on the meridian itself. That creates more uncertainty.

Apart from the visual findings, what else can clue you in that a patient may need to give up their keys? While ophthalmologists certainly aren’t neurocognitive specialists, you may notice a patient having difficulty following a conversation during the exam. A patient may mention in passing some driving incident that occurred. These may prompt you to think about whether the patient is safe behind the wheel.

I’ve also found that family members can be great resources for providing insight on your patients. Involving them in conversations, if they accompany the patient to the exam or if the patient gives you permission to call them, may reinforce any potential discussion, and family members can also help the patient navigate the web and find driving rehabilitation and low-vision resources (more on that below). Many times, I’ve had patients go into an exam room, and the trailing family member says to me softly, “I don’t think my mom’s safe to drive.” That’s not at all uncommon. Family members will occasionally tip you off. They don’t want to be the “bad guy,” and that’s totally reasonable to me, especially since they aren’t the expert that can answer this question.

**Are You Ready for the Talk?**

Patients will be understandably distraught at being told they should alter their driving habits or perhaps stop driving altogether. Naturally, these conversations are challenging and emotionally charged. No patient goes to the doctor wanting to be told they shouldn’t drive. The discussion involves not just questions of logistics for the patient and the inconvenience, but also how patients view themselves as independent people. It brings up issues of personhood and personal freedom, which I sympathize with.

In general, ophthalmologists in residency aren’t trained in great detail about having hard conversations. One book I’ve found useful...
in my practice is *Difficult Conversations.* It’s one of many resources that focus on how to have these discussions. Some takeaways I’ve gleaned include beginning conversations without defensiveness, listening for the meaning of what the patient isn’t saying, staying balanced in the face of attacks and accusations and moving from emotion to productive problem solving. Easier said than done. However, keeping these in mind may make these discussions go smoother, which is beneficial for everyone involved.

As far as timing goes, my own experience talking with patients suggests that conversations about driving are best undertaken gradually. Having the full conversation in a single day can be very challenging. Some patients just aren’t able to process it all or they stop processing once they hear the bad news. I’ve found I haven’t had a lot of success convincing patients not to drive just by saying it’s the law. I often mention my concerns for their own physical wellbeing—notably, elderly drivers are more likely to be fatally injured in a crash than younger drivers. However, I find that doesn’t often change minds. I live in Pennsylvania, where there’s a lot of litigation, so I often bring up the idea of lawsuits to patients. I point out that even if they were involved in an accident that wasn’t their fault, but someone got wind of the fact that they had vision issues, that person might try to make their lives difficult from a legal perspective. That, I think, starts to turn heads because people fear lawsuits, often with good reason.

Sometimes, I’ll mention that, depending on where you live, the doctor may be legally required to report patients who don’t meet the state’s requirements for driving. I don’t think it’s at all common for an ophthalmologist to get in trouble in this regard, though I’m not an expert on case law. In general, it’s good to follow legal guidelines when possible. If a patient commits to me that they’re not going to drive, and I find that credible, I document that conversation in the chart and that they’re not going to drive. Documentation always helps.

If I’m truly concerned that a patient is still driving, and I think they truly present a risk to others, I show them their visual field loss on a screen and point out that a small child could fit within that field loss. I don’t want to be mean to patients, but I also want to help them understand that my true concern is not just for them, but for everyone else. I think it helps patients consider that they have an obligation to society. If that doesn’t move the patient—that they may be putting others in harm’s way—sometimes that moves me to report them, but it’s very uncommon in my practice for that to be necessary. Most patients understand and are reasonable.

Some doctors may argue that this gets into the question of their responsibility being only to the patient. While we have a commitment to the patient in front of us, that same patient who I’m committing to may run over one of my other patients in the waiting room on their way out of the parking lot. So, I feel we have a societal responsibility not to let unsafe situations persist.

**Help Is Out There**

Vision loss doesn’t necessarily mean an end to driving outright. Many states allow those with a certain level of low vision to drive, with some restrictions such as using only secondary roads, not driving during rush hour or on crowded roads, driving only between the hours of 10:00 AM and 2:00 PM or driving only a certain number of miles.

Here are some options for your patients:

- **Occupational therapy.** Patients may need support from practitioners in other fields. Occupational therapy or driver rehabilitation can help certain patients learn to drive safely, and if driving is no longer possible, at least the patient will have that knowledge.

- **Bioptic telescope lenses.** If the patient’s state allows this device for driving, bioptic telescope lenses may offer a way to continue driving safely. Pennsylvania recently established a training program and licensing process for individuals to use bioptic telescope lenses to meet the visual acuity standards for driving. According to PA law,
individuals with visual acuity less than 20/100 combined but at least 20/200 in the best-corrected eye are eligible to apply for a biopic telescope learner’s permit.8

- Uber, Lyft and other ride-share programs. These options may present financial and logistical challenges for elderly drivers, but they can help patients get to appointments, the market and their social engagements.

- Paratransit. This provision is available through the Americans with Disabilities Act of 1990: Section 504 of the Rehabilitation Act. It’s not always fast or convenient, but it’s often an affordable and effective option.

It may be helpful for patients’ recollection after the conversation to keep a printed list of the vision requirements for driving in your state handy, as well as a list of low vision or occupational therapy specialists (state programs are often very good), driver rehabilitation programs, alternative transportation options and social workers in your area.

Final Thoughts
Glaucoma increases the risk of being involved in a car accident, especially for patients over the age of 75. That doesn’t mean your patients shouldn’t drive, but they should be made aware of the increased risk, which is present even in patients without severe field loss, and that extra care on the road may be required.4


ABOUT THE AUTHOR
Dr. Myers is chief of the Wills Eye Glaucoma Service and a professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University in Philadelphia.
**INTRAOCULAR LENSES**

**Nighttime is the Right Time for a New IOL**

Johnson & Johnson Vision recently announced availability of the presbyopia-correcting intraocular lens, the Tecnis Symfony OptiBlue IOL powered by InteliLight technology. The company says that the extended depth-of-focus lens expands presbyopia correction to more patients and joins the Tecnis Synergy IOL, a hybrid lens designed for spectacle independence, in the company’s InteliLight portfolio.

The company explains that InteliLight is a combination of three Johnson & Johnson Vision proprietary technologies: a violet-light filter; echelette design; and achromatic technology. The technology was first introduced in the Tecnis Synergy IOL.

The company says the violet-light filter blocks the shortest wavelengths of light that produce the most light scatter, which it says helps mitigate halo, glare and starbursts, and minimizes visual disturbances when driving at night. The echelette design helps reduce light scattering and halo intensity, making it easier to see digital devices, according to J&J. And the lens’s maker says the achromatic technology corrects chromatic aberration for better contrast day and night and helps give good vision at various distances. The company says the new lenses are aimed to be especially useful in terms of low-light performance and providing contrast.

The Symfony mitigates the effects of presbyopia by providing an extended depth of focus, J&J explains. Compared with an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The lenses in the portfolio, Tecnis Synergy IOL and Tecnis Symfony OptiBlue IOL, are also available in Toric II versions. To learn more about the InteliLight portfolio, you can visit [www.jnjvisionpro.com/intelilight](http://www.jnjvisionpro.com/intelilight).

**DRY EYE**

**A Portable Device Worth Its Salt**

Trukera Medical, formerly known as TearLab, says its ScoutPro osmolarity system helps increase the convenience and efficiency of dry-eye screening.

Performing objective tests for patients experiencing possible signs or symptoms of dry eye can help them receive timely and proper treatment, the company says. One metric to help diagnose and determine the severity of the condition is tear osmolarity. Several osmometers exist in the United States, but the ScoutPro deviates from its competitors as the first handheld version, according to the company. The device’s maker says that the ScoutPro enables both nanoliter volume sample collection and analysis to be performed from anywhere in the practice and offers quick test results “in the palm of your hand.”

The device is rechargeable with a battery life of eight hours. The charging base takes up less shelf space than some others and comes with an optional wall mount, Trukera says. The top of the ScoutPro uses what the company calls “VeriLyte technology” for specimen collection and analysis. The small screen on the device displays results shortly after each test and can store the recent scores. Trukera’s website also notes that the test cards are interchangeable with those in the first-generation TearLab osmolarity system.

For more information, visit [trukera.com](http://trukera.com).

**AMBLYOPIA**

**Treating Amblyopia at Home**

Eye patching for amblyopia is associated with a handful of adverse effects in children, including skin irritation, low self-esteem and noncompliance. In response to the desire for alternative treatments, NovaSight recently announced the FDA clearance of its new eye-tracking-based amblyopia treatment device, called CureSight. Developers say the device, designed for at-home use, helps amblyopic eyes learn to work simultaneously while a video of the child’s choice is streamed through the red-blue treatment glasses.

The treatment works by blurring the center of vision of the image shown to the strong eye, encouraging the brain to complete the image’s fine details and consequently training both eyes to work as a team, according to the company. Children are required to complete four months of treatment, with a minimum of 18 hours per month. The device’s cloud-server connection allows for remote monitoring of treatment reports by the patient’s
eye-care provider via a web portal.

The company also says that the treatment can be billed through three CPT codes, which will perhaps make it accessible to a broader range of patients.

For more information, visit nova-sight.com.

▶ RETINAL SURGERY

**CryoSurgery in the Palm of Your Hand**

CryoTreq, a new product for treating retinal tears and detachments from BVI, debuted this year at the American Academy of Ophthalmology Meeting in Chicago for U.S. surgeons.

The cryo-based product is a handheld, stand-alone, single-use device for minimally invasive **ab externo** cryo-surgery. BVI says it requires no external connections to equipment, gas tanks or power and doesn’t require any service or maintenance. The device is hand-controlled with a single button that activates it. Its probe reaches temperatures as low as -88 degrees Celsius and cryogenic temperatures within four to six seconds.

To learn more, visit cryotreq.bvimedical.com.

▶ VISION TESTING

**Heru Adds Dark Adaptation**

Heru’s wearable AMD vision testing platform has a new add-on modality to help clinicians catch early signs of age-related macular degeneration in their patients—a dark adaptation test.

The non-invasive test takes about four and a half minutes for the rapid exam and about 20 minutes for the extended exam, the company says. The test is billable to insurance with a national reimbursement average of $58.83, according to Heru. The company also notes that it’s co-billable with visual fields, optical coherence tomography, fundus imaging and/or office visits, and has multiple supported ICD-10 codes. The wearable device also includes contrast sensitivity, visual field and color vision tests.

For information, visit seeheru.com/technology.

▶ DRUGS

**Anesthetic Gel Approved**

Iheezo (chloroprocaine hydrochloride ophthalmic gel) 3% was recently approved by the FDA for ocular surface anesthesia. Harrow and Sintetica say the sterile, single-patient-use, physician-administered, preservative-free gel was shown to be safe and effective in three human clinical trials. In one study, effect was achieved in about one to one and a half minutes and provided sufficient anesthesia to perform a surgical procedure lasting 22 minutes, on average. The company points out that none of the patients in this study required supplemental anesthesia to complete the procedure. They also note that the single-use packaging may decrease risk of infection and medication errors associated with communal eye drops. The commercial launch is expected ahead of the 2023 ASCRS Meeting in San Diego.

For information, visit harrowinc.com.

**Compounded Antibiotic to Debut**

ImprimisRx is launching a new compounded antibiotic called Fortisite—which combines tobramycin 1.5% and vancomycin 5%. As part of the company’s Patient Access Program, ImprimisRx says that it will offer a 100-replacement guarantee for any expired 503B Fortisite product. The formulation can last for up to 180 days when kept refrigerated at a temperature of 5 degrees Celsius, according to a company press release.

The antibiotic is now available for order by patients through the ImprimisRx 503A pharmacy, the company says. Physicians will be able to stock Fortisite in their clinics once it’s available through the ImprimisRx 503B outsourcing facility, which is expected to happen in the first half of 2023.

For information, visit https://sf.imprimisrx.com/s/fortisite.com.

**A Lucentis Alternative**

Coherus BioSciences announced the commercial availability, beginning last month, of Cimerli (ranibizumab-eqrn), a biosimilar product “interchangeable” with Lucentis (ranibizumab injection) for all of Lucentis’ approved indications. Cimerli is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab products or any of the excipients in Lucentis and Cimerli. Hypersensitivity reactions may manifest as severe intraocular inflammation, Coherus says.

Cimerli is available through specialty distributors for $1,360 and $816 per single-dose vial for the 0.5 mg and 0.3 mg dosages, respectively.

For information, visit cimerli.com.
Treatment for Advanced Glaucoma Analyzed

Researchers compared visual field progression between the two arms of the Treatment of Advanced Glaucoma Study (TAGS), as part of a post hoc analysis of VF data from a two-arm multicenter randomized controlled clinical trial.

A total of 453 patients with newly diagnosed advanced open-angle glaucoma in at least one eye from 27 centers in the United Kingdom were randomized to either trabeculectomy (n=227) or medications in their index eye (n=226) and followed-up for two years with two 24-2 VF tests at baseline, four, 12 and 24 months.

Average difference in rate of progression (RoP) was analyzed using a hierarchical Bayesian model. Time for each eye to progress from baseline beyond specific cutoffs (0.5, 1, 1.5 and 2 dB) was compared using survival analysis.

A total of 211 eyes in the trabeculectomy-first arm and 203 eyes in the medications-first arm were analyzed. Here are some of the findings:

- The average RoPs (estimate [95 percent credible intervals]) were:
  - -0.59 (-0.88 to -0.31) dB/year in the medications-first arm and -0.40 (-0.67 to -0.13) dB/year in the trabeculectomy-first arm.
  - The difference wasn’t significant (Bayesian p=0.353).
  - More eyes progressed in the medications-first arm: ≥0.5 dB (p=0.001), ≥1 dB (p=0.014), ≥1.5 dB (p=0.071) and ≥2 dB (p=0.061).

Researchers found no significant difference between the two arms in TAGS in the average RoP at two years.

**Vascular Density in DR**

Investigators assessed choroidal vascularity by diabetic retinopathy stage using the choroidal vascular density (CVD) obtained from swept-source optical coherence tomography en face images.

This prospective, cross-sectional, multicenter study included patients from Niigata City General Hospital and Saiseikai Niigata Hospital between October 2016 and October 2017. CVD was obtained by binarizing SS-OCT en face images.

Patients were allocated to the healthy control (n=28), no DR (n=23), nonproliferative DR without diabetic macular edema (n=50), NPDR+DME (n=38), and proliferative diabetic retinopathy or any previous treatment with panretinal photocoagulation (n=26) groups. Here are some of the findings:

- Investigation of the choriocapillaris slab level indicated the no-DR group had significantly high CVD values (p<0.05) and PDR groups had significantly low CVD values (p<0.01).
- Investigation of the large choroidal vessel level indicated that the NPDR+DME and PDR groups had significantly lower CVD values than the control group (p<0.05 and p<0.01, respectively).

**Biomarkers for Wet AMD**

Researchers identified optical coherence tomography biomarkers, including thin and thick double layer signs (DLS) for progression from intermediate AMD (iAMD) to exudative macular neovascularization (MNV) over 24 months, as part of a retrospective cohort study conducted at Retina Consultants of Texas.

A total of 458 eyes of 458 subjects with iAMD in at least one eye with 24 months of follow-up data were included.

The following biomarkers were assessed at baseline: high central drusen volume (≥20.03 mm³); intraretinal hyperreflective foci (HRF); subretinal drusenoid deposits; hyporeflective drusen cores; thick/thin DLS; and central choroidal thickness.

Here are some of the findings from the analysis:

- During follow-up, 18.1 percent (83/458) of eyes with iAMD progressed to exudative MNV.
- Thick DLS, HRF and fellow eye exudative MNV were found to be independent predictors for the development of exudative MNV within two years.
- Baseline frequencies, odds ratios, 95 percent confidence intervals and p-values for these biomarkers were as follows:
  - thick DLS (9.6 percent: 4.339; CI, 2.178 to 8.644; p<0.001);
  - HRF (36 percent: 2.340; CI, 1.396 to 3.922; p=0.001); and
  - fellow eye exudative MNV (35.8 percent: 1.694; CI, 1.012 to 2.837; p=0.045).

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Researchers determined thick DLS, HRF and fellow-eye exudative macular neovascularization were associated with an increased risk of progression from iAMD to exudative MNV.
A teenager is referred to the Wills Eye Oncology Service for lid swelling and drooping.

Leo M. Hall, MD, MS, Sara E. Lally, MD, Carol L. Shields, MD, and Tatyana Milman, MD
Philadelphia

Presentation
A 14-year-old Caucasian male noted left upper eyelid swelling and droopiness that he attributed to allergies. After seven months, he presented to his local ophthalmologist due to progressive swelling. Magnetic resonance imaging of the orbits demonstrated a left lacrimal gland mass. The patient underwent incisional biopsy. Pathology revealed a pleomorphic adenoma (PA). The patient was referred to the Wills Eye Hospital Ocular Oncology Service for further management.

Medical History
Past medical history was non-contributory. Family history was notable for leukemia in the paternal grandfather, stroke in the maternal grandmother and grandfather, and hypertension in the maternal grandmother. Social history was non-contributory. The patient did not take any medications, nor did he demonstrate medication allergy.

Examination
Upon presentation to Wills’ Ocular Oncology Service, visual acuity was 20/20 in both eyes. The pupils were round, symmetric, equal and reactive to light OU. Extraocular motility and confrontational visual fields were full bilaterally. Intraocular pressure was within normal limits. Color plates were full OU.

External examination demonstrated a well-healed superior lid crease wound with 3 mm of left blepharoptosis and a palpable mass in the left superolateral orbit. There was 5 mm of painless proptosis and inferonasal displacement of the globe. Anterior examination of both eyes was within normal limits. Dilated fundoscopic examination of both eyes was unremarkable with no optic nerve edema, pallor or tortuous vessels.

What’s your diagnosis? What further work-up would you pursue? The diagnosis appears on the next page.
Work-up, Diagnosis and Treatment

Review of initial orbital MRI revealed a circumscribed left lacrimal gland mass with bosselations (irregular surface) and no bony erosion (Figure 1). The differential diagnosis included lacrimal gland pleomorphic adenoma, adenoid cystic carcinoma, lymphoid hyperplasia or lymphoma, dermoid cyst, and inflammatory conditions like sarcoidosis or dacryoadenitis (inflammatory pseudotumor). Review of histopathology confirmed the diagnosis of pleomorphic adenoma. Subsequently, complete surgical excision of the mass via lateral orbitotomy approach was recommended.

Surgical approach revealed the large lacrimal gland mass with orbital scarring from the previous incisional biopsy. The mass was completely excised. Histopathology confirmed pleomorphic adenoma with no evidence of malignancy.

Periodic follow-up MRIs were performed to monitor the site, given the previous incisional biopsy. At 29 months follow up, increasing ptosis was noted. Repeat MRI revealed concern for recurrent left lacrimal gland tumor. Orbitotomy and pathology revealed recurrent pleomorphic adenoma with no evidence of malignancy. Given the recurrence, stereotactic radiotherapy (SRT) (25 Gy) was performed to the superior and lateral orbit. Repeat MRI 2.5 years after SRT demonstrated a second recurrence in the superior medial orbit. Surgical resection and histopathology demonstrated multifocal recurrent pleomorphic adenoma, but with transformation to cellular atypia, composed of variably cellular tumor nodules (Figure 2). The patient received SRT (25 Gy) to the medial half of the orbit. Six months later, MRI scan again noted a recurrent mass in the inferior temporal orbit, which was surgically removed, and histopathology demonstrated multifocal pleomorphic adenoma with foci of transformation to carcinoma ex pleomorphic adenoma (CXPA) (Figure 3). After discussion of management options with the patient and at a multidisciplinary tumor board, a recommendation for orbital exenteration was suggested and performed.

Discussion

Lacrimal fossa lesions represent more than 10 percent of all orbital space-occupying lesions. Despite its overall rare prevalence, pleomorphic adenoma, also termed benign mixed tumor, is the most common benign epithelial neoplasm of the lacrimal gland. Pleomorphic adenoma often presents in the fourth decade with no appreciable—or possibly slight male—sex predilection. Patients present classically with longstanding painless proptosis and inferonasal displacement of the globe. Imaging demonstrates a well-circumscribed mass in the lacrimal gland fossa, which may be associated with bone remodeling, without bony erosion or destruction.

Histopathologically, pleomorphic adenoma is pseudoencapsulated and consists of bilayered epithelial-myoe-
epithelial ductules in the background of myoepithelial cell proliferation and variably myxoid and cartilaginous stroma. Foci of squamous differentiation can be seen. Dense cellularity, cytologic atypia, mitotic figures, and necrosis are not features of benign pleomorphic adenoma. Incompletely excised tumors tend to recur in a multifocal, multinodular fashion, no longer bounded by a pseudocapsule. Pleomorphic adenomas commonly demonstrate overexpression of the pleomorphic adenoma gene 1 (PLAG1) or high-mobility group AT-hook 2 (HMGA2) genes, which correspond to underlying PLAG1 and HMGA2 gene rearrangements. Immuno-histochemically, PLAG1 nuclear staining is highly specific for pleomorphic adenoma.

In most cases, pleomorphic adenoma demonstrates an indolent course and is cured with complete excision. However, malignant transformation (CXPA, or malignant mixed tumor) has been reported in 1.5 to 13.8 percent of pleomorphic adenomas. Malignancy can arise spontaneously or in a setting of recurrence following incomplete excision. Although some experts contest a strict “no incisional biopsy” dogma, consensus remains in favor of complete primary excision of the tumor with intact pseudocapsule without biopsy. According to some studies, CXPAs are more frequent in males. Patients typically present with proptosis, orbital ache, palpable mass and reduced ocular motility. Imaging can demonstrate an infiltrative mass with bony erosion.

At a microscopic level, CXPAs can show patchy to complete hyalinization (“mummification”), invasion into the surrounding myxoid stroma, and necrosis. The carcinoma component can be of any type in CXPA. In lacrimal CXPA, lacrimal duct adenocarcinoma is the most common CXPA. Myoepithelial carcinoma XPA is relatively rare. These tumors can demonstrate underlying molecular genetic rearrangements in PLAG1 and HMGA2 genes, similar to their precursor pleomorphic adenoma, which may aid in the diagnosis in challenging cases. Prognosis is based on the following criteria: 1) in situ carcinoma (intracapsular); 2) minimally invasive (<1.5 mm); and 3) invasive (≥1.5 mm). Treatment is ultimately rendered based on histopathologic findings and disease staging, and largely consists of surgical excision, exenteration or radiation therapy. One retrospective study showed that patients who underwent complete excision with pseudocapsule intact have greater survival as compared to those who underwent debulking and radiation therapy.

Our case highlights the importance of initial complete surgical resection of pleomorphic adenoma. Incomplete excision is a risk for multifocal recurrence, which is extremely difficult to manage and poses a risk for malignant transformation. Long-term follow up of patients who have undergone resection of pleomorphic adenoma with clinical examination and MRI is prudent. New onset blepharoaphtalmosis, proptosis, pain or dysmotility or MRI findings of a recurrent mass should raise consideration for CXPA.
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MA-0151PA

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