Accurately evaluating a patient's status and the risk that the disease will get worse is critical for choosing the most appropriate treatment.
Focus on innovation with DEXYCU®
(dexamethasone intraocular suspension) 9%

Learn more at DEXYCU.com
Accurately evaluating a patient’s status and the risk that the disease will get worse is critical for choosing the most appropriate treatment. P. 32
XEN® helps put the power to control her IOP in your hands

The XEN® Gel Stent is minimally invasive filtering surgery that achieves powerful reduction of intraocular pressure (IOP),

- From a wide range of baseline pressures, XEN® achieved a mean IOP of 15.9 (± 5.2) mm Hg through 12 months (n = 52).
- 76% of XEN® patients achieved a ≥ 20% IOP reduction in the ITT group (N = 65).
- 81% of XEN® patients achieved a ≥ 25% IOP reduction among those completing the 12-month visit (n = 52).
- Pivotal safety data included 0% intraoperative complications (0/65) and 0% persistent hypotony; transient hypotony occurred in 24.6% of patients (16/65).

INDICATIONS

The XEN® Glaucoma Treatment System (XEN® 45 Gel Stent preloaded into a XEN® Injector) is indicated for the management of refractory glaucomas, including cases where previous surgical treatment has failed, cases of primary open-angle glaucoma, and pseudoxfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XEN® Gel Stent is contraindicated in angle-closure glaucoma where angle has not been surgically opened, previous glaucoma shunt/valve or conjunctival scarring/pathologies in the target quadrant, active inflammation, active iris neovascularization, anterior chamber intraocular lens, intraocular silicone oil, and vitreous in the anterior chamber.

WARNINGS

XEN® Gel Stent complications may include choroidal effusion, hyphema, hypotony, implant migration, implant exposure, wound leak, need for secondary surgical intervention, and intraocular surgery complications. Safety and effectiveness in neovascular, congenital, and infantile glaucoma has not been established. Avoid digital pressure following implantation of the XEN® Gel Stent to avoid the potential for implant damage.

PRECAUTIONS

Examine the XEN® Gel Stent and XEN® Injector in the operating room prior to use. Monitor intraocular pressure (IOP) postoperatively and if not adequately maintained, manage appropriately. Stop the procedure immediately if increased resistance is observed during implantation and use a new XEN® system. Safety and effectiveness of more than a single implanted XEN® Gel Stent has not been studied.

ADVERSE EVENTS

The most common postoperative adverse events included best-corrected visual acuity loss of ≥ 2 lines (≤ 30 days 15.4%; > 30 days 10.8%; 12 months 6.2%), hypotony IOP < 6 mm Hg at any time (24.6%), no clinically significant consequences were associated with hypotony, such as choroidal effusions, suprachoroidal hemorhage, or hypotony maculopathy.

Please see accompanying full Directions for Use or visit https://www.rxabbvie.com/pdf/xen_dfu.pdf

The need to use routine antibiotic prophylaxis to prevent endophthalmitis following cataract surgery—and how such prophylaxis should be accomplished—remains controversial due to a lack of level-1 evidence. Nevertheless, antibiotic prophylaxis is universally used by cataract surgeons.

Recently, responses to an online survey from 1,205 members of the American Society of Cataract and Refractive Surgery revealed shifting patterns in cataract surgeons’ use of the different options for endophthalmitis prevention. (Similar surveys were done in 2007 and 2014.) Findings from the current survey include:

- Sixty-six percent of cataract surgeons are using intracameral antibiotics (compared to 50 percent in 2014 and 30 percent in 2007). Of those using IC antibiotics, 38 percent started doing so within the past two years.
- Only 5 percent of cataract surgeons are now using irrigation bottle infusion or subconjunctival injection to deliver the antibiotic.
- For those U.S. surgeons using intracameral antibiotics, the choice of antibiotic has shifted dramatically since the 2014 survey. Use of vancomycin dropped from 52 percent in 2014 to 6 percent today; moxifloxacin use jumped from 31 percent in 2014 to 83 percent today.
- How the intracameral antibiotic solution is prepared has shifted. In 2007, 77 percent of surgeons had operating room nurses mix the solution; only 18 percent of surgeons relied on a compounding pharmacy. Today, only 44 percent have an OR nurse prepare the solution, while 45 percent now rely on a compounding pharmacy.
- Use of preop and postop topical antibiotic drops has decreased as intracameral use has increased. Preop antibiotic drops were used by 85 percent of survey respondents in 2014; that’s dropped to 73 percent currently. In 2014, 97 percent of cataract surgeons used postop antibiotic drops; that number is now 86 percent. In fact, according to the new survey, 24 percent of surgeons using intracameral antibiotics aren’t using postoperative drops at all.
- Among surgeons not using intracameral antibiotics, 66 percent cited concerns about risks associated with mixing or compounding the antibiotic as their reason; 48 percent didn’t see it as necessary; and 42 percent cited cost as the reason.
- If a commercially approved IC antibiotic were available, 93 percent say they’d be using it.

David F. Chang, MD, a clinical professor at the University of California, San Francisco, and in private practice in Los Altos, California, reported on the survey results in a recent publication. He notes that the results of the survey are significant. “There were approximately 1,200 respondents for each of the 2007, 2014 and 2021 ASCRS member surveys, making them among the largest surveys ever conducted on surgical antibiotic prophylaxis,” he says. “In addition, identical questions were posed whenever possible in all three surveys, which provides a way to evaluate changing trends in practice patterns over time.”

(Continued on p. 6)
We’ll go first

Innovation is at the core of everything we do. At Glaukos, we push the limits of science and technology to solve unmet needs in chronic eye diseases.

Experience a world of firsts in vision care.
Learn more at Glaukos.com.
Infection-prevention Survey

(Continued from p. 3)

most striking trends revealed by the data. “To see usage of intracameral antibiotic injection continuing to increase over time—to now almost two out of every three surgeons—is a very compelling trend, given the lack of any approved commercial solutions in the U.S. and in so many other countries,” he says. “This probably reflects the growing body of evidence that has mostly come in the form of large retrospective trials. The second striking trend is the shift to moxifloxacin preference (83 percent of U.S. surgeons, compared to 31 percent in 2014) and away from vancomycin (6 percent of U.S. surgeons, compared to 52 percent in 2014). This was undoubtedly driven by recognition of the rare but devastating complication of HORV [hemorrhagic occlusive retinal vasculitis] associated with vancomycin, along with new studies on moxifloxacin safety and efficacy. “Finally, there was a decrease in the use of topical pre- and postoperative antibiotic prophylaxis,” he notes. “This was mainly among surgeons employing intracameral antibiotics, where one out of four didn’t add topical antibiotics. As many as half of all surgeons would drop, or consider dropping, the topical antibiotic if a commercial intracameral antibiotic were approved.”

Asked how these survey results might affect clinical practice, Dr. Chang points out that although endophthalmitis is very rare, medico-legal considerations are a factor in every clinician’s decision-making. “Those using compounding pharmacies or using Vigamox solution off-label for their intraocular moxifloxacin source can defend these practices based on their use by a significant percentage of cataract surgeons, as documented in this most recent survey,” he notes. “In addition, I believe that many ophthalmologists already using intracameral antibiotic prophylaxis may have been hesitant to discontinue topical antibiotics, for fear that their use was still the community standard. This survey, in which half of the respondents seemingly question the necessity of topical antibiotics in addition to intracameral injection, should allay that concern.”

ASCRS and the U.S. Veterans Health Administration are now working to organize a multicenter, prospective randomized clinical trial in the United States to provide some level-1 evidence to help guide surgeons in their choice of how to manage this. The Topical vs. Intracameral Moxifloxacin to Prevent Endophthalmitis study will compare the efficacy of intracameral moxifloxacin to topical moxifloxacin alone.


Trend Analysis and Glaucoma Progression Rate

In advanced glaucoma, where there is considerable risk of developing visual disability, estimating the rate of progression is vital. However, researchers in Osaka, Japan, believe that trend analysis of visual field (VF) global indices may underestimate the rate of progression in advanced glaucoma due to the influence of test points without detectable sensitivity or blind locations. 1

To test this hypothesis, they compared the rates of change of VF global indices with and without exclusion of undetectable points at various disease stages. They also developed targeted mean total deviation, an average of total deviation values that excludes undetectable locations. The results demonstrated that MD rate of progression is lower in severe glaucoma compared with earlier stages, and this apparent reduction becomes smaller if consistently undetected VF locations are removed.

The study assessed 648 eyes of 366 glaucoma patients with eight or more reliable 30-2 standard automated perimetry tests taken over more than two years. Targeted mean total deviation was calculated as the average of the total deviation values after excluding locations that were consistently undetected (i.e., had a threshold sensitivity value of <0 dB). Eyes were classified as early (≥6 dB), moderate (-6 dB to -12 dB), advanced (-12 dB to -20 dB) and severe (<-20 dB) based on baseline MD. The rates of change of MD and tar-

(Continued on p. 8)
Choose the surgeon-preferred DuoVisc® OVD system, powered by chondroitin sulfate.¹-⁴

Experience the superior endothelial protection of VISCOAT® OVD and the excellent space maintenance of ProVisc® OVD in one versatile OVD system designed to meet your advanced surgical needs.¹-³, ⁵-⁷, †

References
3. Lindstrom RL, Ong M. Protective effect of OVDs against hydrogen peroxide-induced oxidative damage to corneal endothelial cells: in vitro model. Presented at ASCRS, 26 Mar 2011, San Diego, CA. ⁴
5. DuoVisc® Package Insert.

For Important Product Information, please see adjacent page.

†VISCOAT® showed significantly lower superior corneal endothelial cell loss at 16 weeks post-op compared to HEALON*; n=59, P=0.01.

*Trademarks are the property of their respective owners.
Important Product Information for DUOVISC® OVD

Description: DuoVisc® Viscoelastic System is designed to provide two viscoelastic materials with different physicochemical properties that can be used differently and/or sequentially to perform specific tasks during a cataract procedure. DuoVisc® Viscoelastic System consists of VISCOAT® Ophthalmic Viscosurgical Device and ProVisc® Ophthalmic Viscosurgical Device. Caution: Federal (USA) law restricts this device to sale by, or on the order of, a physician.

Description: VISCOAT® (Sodium Chondroitin Sulfate – Sodium Hyaluronate) Ophthalmic Viscosurgical Device. Indications: VISCOAT® OVD is indicated for use as an ophthalmic surgical aid in anterior segment procedures including cataract extraction and intracocular lens (IOL) implantation. VISCOAT® OVD maintains a deep anterior chamber during anterior segment surgeries, enhances visualization during the surgical procedure, and protects the corneal endothelium and other ocular tissues. The viscoelasticity of the solution maintains the normal position of the vitreous face and prevents formation of a flat chamber during surgery. Warnings/Precautions: Failure to follow assembly instructions or use of an alternate cannula may result in cannula detachment and potential patient injury. Precautions are limited to those normally associated with the surgical procedure being performed. Although sodium hyaluronate and sodium chondroitin sulfate are highly purified biological polymers, the physician should be aware of the potential allergic risks inherent in the use of any biological material. Adverse Reactions: VISCOAT® OVD has been extremely well tolerated in human and animal studies. A transient rise in intraocular pressure in the early postoperative period may be expected due to the presence of sodium hyaluronate, which has been shown to affect such a rise. It is therefore recommended that VISCOAT® OVD be removed from the anterior chamber by thorough irrigation and/or aspiration at the end of surgery to minimize postoperative IOP increases. Do not overfill anterior chamber. ATTENTION: Please refer to the Directions for Use for a complete listing of indications, warnings and precautions.

Description: ProVisc® (Sodium Hyaluronate) Ophthalmic Viscosurgical Device. Indications: ProVisc® OVD is indicated for use as an ophthalmic surgical aid in the anterior segment during cataract extraction and intracocular lens (IOL) implantation. Ophthalmic viscoelastics serve to maintain a deep anterior chamber during anterior segment surgery allowing reduced trauma to the corneal endothelium and surrounding ocular tissues. They help push back the vitreous face and prevent formation of a flat chamber during surgery. Warnings/Precautions: Postoperative increases in intraocular pressure have been reported with sodium hyaluronate products. The IOP should be carefully monitored and appropriate therapy instituted if significant increases should occur. It is recommended that ProVisc® OVD be removed by irrigation and/or aspiration at the close of surgery. Do not overfill anterior chamber. Although sodium hyaluronate is a highly purified biological polymer, the physician should be aware of the potential allergic risks inherent in the use of any biological material; care should be used in patients with hypersensitivity to any components in this material. Cannula assembly instructions should be followed to prevent patient injury. Adverse Reactions: Postoperative inflammatory reactions such as hypopyon and iritis have been reported with the use of ophthalmic viscoelastics, as well as incidents of corneal edema, corneal decompensation, and a transient rise in intraocular pressure. ATTENTION: Please refer to the directions for use for a complete listing of indications, warnings and precautions.

Trend Analysis (Continued from p. 6)

geted mean total deviation in each stage were statistically compared. Overall, targeted mean total deviation rate of change strongly correlated with MD rate of change. However, the MD slope (-0.34 dB/year) in severe glaucoma was significantly less steep than the targeted mean total deviation slope (-0.42 dB/year) and was less steep than MD slopes in the other stages. The researchers noted that this difference between MD and targeted mean total deviation slopes was most prominent in eyes with MD values less than -25 dB.

“The number of undetectable locations increased as MD decreased (worsened), and more than half of locations were already undetected in baseline tests in severe glaucoma,” they wrote in their paper. “These results support our hypothesis that the lower rate of MD slopes in severe glaucoma is caused by the presence of consistently undetectable, and thus non-progressive, locations.”

On the other hand, MD slope was significantly faster than targeted mean total deviation slope in early and moderate glaucoma. The researchers suggested the small but significant difference between targeted mean total deviation rate of change and MD rate of change in earlier stages may have resulted from the fact that MD is more heavily weighted in central locations while targeted mean total deviation is not.

“It seems clear that conventional MD slope that shows positive slopes in 67 percent of cases with MD values less than -25 dB is not appropriate for estimating the rates of progression in these eyes, and targeted mean total deviation slopes may be a promising alternative,” the researchers concluded.

Important Product Information for DUOVISC® OVD

Trend Analysis (Continued from p. 6)

Light Exposure and the Eye

A study from Israel measured the effect of indoor light intensity on a group of preschool children.1

The study enrolled 1,131 children between the ages of 4 and 5 from schools in which light intensity ranged from 264 to 804 lux. Based on the level of light, researchers placed the participants in three groups: low illuminance (330 kids, 29 percent), medium illuminance (434 children, 38 percent) and high illuminance (367 children, 33 percent). The researchers found a significant difference in light intensity among the three groups: 359 ±0.64 lux in the low illuminance group, 490 ±0.21 lux in the medium illuminance group and 670.76 ±3.73 lux in the high illuminance group.

Of note, the mean spherical equivalent was 0.56 ±0.03 D in the low-intensity group, 0.73 ±0.03 D in the medium-intensity group and 0.89 ±0.03 D in the high-intensity group. About 42 percent of kids in the low-intensity group had zero refraction or minus compared with 19 percent of children in the high-intensity group. These findings are consistent with many other studies that linked light exposure to refractive development, with a possible biological link between increased dopamine release by brighter light and the well-documented ability of dopamine agonists to slow axial elongation, making a direct link more plausible, the investigators suggested. They add that if future studies confirm the findings, increasing light intensity in classrooms may help curb myopia development.1


© 2021 Alcon, Inc.
Need Ocular Surface Repair?*
We’ve Got You Covered!

AcellFX™
Acellular Amniotic Membrane

• Air-dried, not chemically dried
• Ready for immediate use without thawing or rinsing
• Flexible membrane with no ring required
• Convenient storage at room temperature

Learn more at AcellFX.com

*AcellFX is an HCT/P (human cells, tissues, and cellular and tissue-based product) that is intended for homologous use, providing protection or covering in ocular surface repair.
We’re retiring the questions that keep you guessing.

As a global OCT market leader, Topcon Healthcare delivers service the way it should be—filled with responsiveness, honesty, and transparency. Our commitment to service starts before your product is even built. Because we manufacture with ultimate precision that leads to legendary Japanese quality. Others engineer complexity that demands questions. We engineer with simplicity and reliability.

At Topcon Healthcare, we’re in the business of answers.

© 2021 Topcon Healthcare | topconhealthcare.com/questions
32
Glaucoma Staging And Progression Risk Factors
Accurately evaluating a patient’s status and the risk that the disease will get worse is critical for choosing the most appropriate treatment.
Douglas J. Rhee, MD, Stephen Lau, MD, and Yasemin G. Sozeri, MD

28
Patient Selection: Trab, Xen or PreserFlo?
Age, severity of disease and a host of other factors should be considered when choosing a procedure for a particular patient.
Michelle Stephenson
Contributing Editor

38
A Glance at the Dry-eye Pipeline
The number of drops being developed to treat this common ailment continues to grow.
Leanne Spiegle
Associate Editor

44
Is Referral Practice in Your Future?
For young MDs considering their next steps, experts offer their perspectives on tertiary and quaternary care.
Christine Leonard
Senior Associate Editor
3
News

14
EDITOR'S PAGE
Changing Our Prescription
Walter Bethke
Editor in Chief

16
REFRACTIVE/CATARACT RUNDOWN
Lessons Learned from Being an Expert Witness
Good patient care and decreasing your litigation risk go hand in hand.
Lisa Nijm, MD, JD

21
THE FORUM
Uphill, Both Ways, In the Snow
Mark H. Blecher, MD
Chief Medical Editor

22
TECHNOLOGY UPDATE
LIRIC: A Novel LVC Treatment
This non-invasive method of correcting refractive error alters the cornea's index of refraction rather than its shape.
Christine Leonard
Senior Associate Editor

52
RETINAL INSIDER
A Review of Retinitis Pigmentosa
A rundown of retinitis pigmentosa’s etiology, diagnostic findings, and current and future treatment options.
Hiram J. Jimenez-Davila, MD, Rebecca A. Procopio MS, CGC, and Michael A. Klufas, MD

62
GLAUCOMA MANAGEMENT
Fixed-combination Compounded Therapies
Pharmacy-made drops can be an affordable and beneficial option for many of our patients.
Roma Patel, MD, MBA

68
RESEARCH REVIEW

71
WILLS EYE RESIDENT CASE SERIES
A 67-year-old is referred to Wills with periocular swelling and blurry vision.
Pauline Dmitriev, MD, and Jurij Bilyk, MD

73
AD INDEX & CLASSIFIEDS

VISIT US ON SOCIAL MEDIA
Facebook www.facebook.com/RevOphth
Twitter twitter.com/RevOphth
Caring for your patients. Thriving as a business. That’s what matters. And to make that happen, you need a single integrated technology platform—not disparate solutions. Better workflows. Revenue capture. Claims and insurance processing. Interoperability. Plus... a superior way to engage with patients. All from one trusted source, who will be there for the life of your practice.

See what an integrated technology platform can do for you: NextGen.com/1-ophth
Changing Our Prescription

During the holidays, our televisions are inundated with seasonal commercials. For the most part, they just wash over us and don’t get a second thought. This year, however, one stood out to me. In it, we see kids staring glumly out of the windows of various houses and cars, looking out over their gray, undecorated town square. Then, a thought dawns on them, and they begin raiding their homes’ stockpiles of holiday decorations. They then head to the town square and adorn it with non-denominational lights, pine rope and garland, creating a nice scene.

But then you think: Was this really the job of a bunch of children? What kind of oblivious tightwads are running this burg? You could almost see the town council peeking through their blinds, murmuring, “Whew! The suckers did our work for us!” Then they turn and carve their roast beast.

A similar thought occurred to me this past January when the news broke that billionaire Mark Cuban was starting a prescription drug service, named The Mark Cuban Cost Plus Drug Company, in an effort to battle the rising cost of prescription drugs. In describing the company’s mission, Mr. Cuban uses the example of albendazole, a treatment for hookworm, a disease that strikes mostly disadvantaged people. The drug can cost as much as $500 per course, which presents an almost insurmountable financial hardship for someone without the means to pay. Through his service, however, the cost is $33.

In a country where 30-year-old generic drugs can actually increase in price, rather than becoming more affordable, I appreciate what Mr. Cuban is trying to do. But, at the same time, just like watching the kids doing their town council’s job, I wish the people we’ve elect to safeguard the common good could manage to do something about drug prices themselves. Instead of a patchwork of prescription sales services, it would be nice to have a nationwide, consistent system in place to keep drug prices sane.

Will Mr. Cuban’s new prescription drug service give the powers-that-be the kick in the pants necessary to make changes to the unfair prices we force patients to pay for their medicines? Or will it just reinforce laissez-faire behavior, since they’ve learned that if they’re inactive long enough, someone else will step up and do the work for them?

— Walter Bethke
Editor in Chief
Introducing
An easy to use pre-surgical prep kit designed to improve patient outcomes

It’s not just the act of surgery that’s important – it’s the prep and the recovery as well.
Sumitra Khandelwah, MD

Complimentary to any pre-surgical protocol, the 3-step Bruder Sx Pre-Surgical Patient Prep Kit is available for in-office distribution or patient purchase by referral online.

The Bruder Pre-surgical Patient Prep Kit is an easy and affordable way for patients to ‘tune up’ the ocular surface, minimize post-op discomfort and help prevent infection.
Cynthia Matossian, MD

Discover what’s in the kit and the science behind it at brudersx.com/md2022
888-827-8337 • eyes@bruder.com

©2022 Bruder Healthcare Company Alpharetta, GA 30004
Lessons Learned from Being an Expert Witness

Good patient care and decreasing your litigation risk go hand in hand. Here are 11 pearls from an expert medical witness.

Lisa Nijm, MD, JD
Warrenville, Ill.

Being an expert witness is a little bit like being a detective. The job requires putting together a picture of what happened with the patient based on chart notes, diagnostic tests, other records and depositions from witnesses and treating physicians. Based on these clues, an expert witness should be able to determine how the patient got from their presenting condition to where they are today—that is, if the documentation is all there.

In this article, I’ll share some pearls that I’ve gleaned from my experience as an expert witness to help you manage risk more effectively and decrease your risk of litigation.

Risk Management Pearls

According to data from OMIC, between 2016 and 2020, there were 299 cataract claims totaling $3.6 million in defense expenses and $8.16 million in indemnity payments.1 Looking more closely at the data, we can see that as the popularity of premium IOLs continued to rise, so did the number of claims in this subset. Ninety-nine of these claims involved premium IOLs and premium services (mean indemnity payment $263,077; range: $3,000 to $1 million).1 While this is a predictable outcome given the out-of-pocket nature of premium IOLs along with increased patient expectations, this doesn’t have to be the case. Surgeons can decrease their risks of litigation by incorporating the following principles into practice:

1 Document everything appropriately. Reducing your risk of litigation involves returning to the basics of risk management. In fact, one of the first steps is making sure you’ve documented everything appropriately. It’s very difficult for an expert witness to defend you if they don’t have a record that reflects the care you actually provided. Best practices for written documentation lays a paper trail that an expert witness can readily follow, and ideally allows them to come to the same conclusions that you had in caring for the patient. Poor documentation, on the other hand, allows the plaintiff’s expert to make a case that you deviated from the standard of care even if that isn’t what really happened.

Best practices also requires the record be accurate, consistent and comprehensive. Your chart should paint a full picture, not just focus on particular aspects of the patient’s ocular condition. Be sure to include all vital history and exam findings, including pertinent negatives, any documents you reviewed and the tests you ordered—anything that allowed you to logically come to your diagnosis.

Anything included in the chart becomes a matter of record. Be especially aware of the copying and pasting feature of EHRs that allows inaccurate information to be transcribed into the record. Any part of the medical record that’s inaccurate creates an avenue for a plaintiff’s medical expert to question whether you were assessing the patient properly. Similarly, if you or a staff member make a note that doesn’t match up anywhere else in the chart, as long as it’s in the chart, it may be used as evidence against you.

2 Be mindful of your language. The wording you use to describe the patient’s complaint and anything else in the chart also matters. Inflammatory words and partial
For Chronic Eye Conditions

Think Simple

Preservative-Free Formulations*

- No Preservatives
- No Prior Authorizations
- No Coupons or Copays

Now with Simple Pricing

Any **SINGLE** Drug:
NOW only **$19/mo†**

Any **COMBO** Drug:
NOW only **$39/mo†**

Various options consisting of:
**Brimonidine, Dorzolamide, Latanoprost, Timolol**

Scan QR Code or visit:
www.SimpleDrops.com

---

† Months supply can vary based on the dosing regimen prescribed by the doctor
*For professional use only. ImprimisRx specializes in customizing medications to meet unique patient and practitioner needs. ImprimisRx dispenses these formulations only to individually identified patients with valid prescriptions. No compounded medication is reviewed by the FDA for safety or efficacy. ImprimisRx does not compound essential copies of commercially available products. References available upon request.

Simple Drops and ImprimisRx are registered trademarks of Harrow Health Inc.
©2021 ImprimisRx. All Rights Reserved. IMPO0443 06/21
notes out of context may come back to bite you.

Be sure to also communicate this practice to your staff. Both physician and staff should have a mutual understanding of what sort of documentation goes into the chart. Sometimes patients say things off-the-cuff that when documented and read alone create a very different impression than what actually occurred. However, if that’s the only thing written in the chart, it’s accepted as accurate.

3 Never alter anything. As you know, you must never alter medical records. That’s the number-one way physicians get into trouble. You may consult with your insurance carrier if you feel something needs to be added. Most of the time this will be in an addendum that’s signed and dated appropriately. As most malpractice carriers will tell you, the time to add a note to the chart is when the patient is being seen or at their next visit, not when you receive notice that there’s a lawsuit.

4 Review your colleagues’ charts and have them review yours. As a best practice, I’d recommend having a colleague evaluate a chart objectively through the “risk management lens” to identify potential areas of improvement.

Ask them to verify that you’re recording sufficient details that would enable another ophthalmologist to support your clinical decisions. If you’re in a group practice, take one another’s chart every now and then (using a HIPAA-compliant protocol) and ask yourself, “Could I ascertain from this chart that the assessment and treatment were appropriate? That the patient’s issues were taken care of? Does the treatment provided adhere to the standard of care based on the way the patient is presented in the chart?”

5 Try a variety of patient teaching methods. Communication skills are key to mitigating risk. People learn in many different ways, so to ensure your patients have a thorough understanding of premium IOLs and have appropriate expectations, it’s a good idea to supplement your consent discussion with educational handouts, videos and other tools whenever possible. For instance, I routinely use an eye model to give patients a 3D visual of what’s going on in their eye and to help explain potential complications.

Even if your patient doesn’t have any questions, using teach-back methods can help you gauge how much your patient really understands about the treatment and what their expectations are. Staff can also help educate patients by asking them to explain in their own words what their surgical goals are, what they expect their vision to be like postoperatively and how the surgery will affect their daily activities. Patients need to understand the risks, benefits and alternatives to any procedure. At times, patients may dismiss cataract surgery as risk-free because the procedure is outpatient or their friends have had great outcomes. Helping them understand that cataract surgery is a surgery and the inherent risks that are present, especially in regard to IOLs, can make a huge difference. Ensuring that patients have realistic expectations—even in regard to premium IOLs—is key.

6 Use comprehensive consent forms. Using a patient-specific consent form as opposed to a standard consent form is another important part of your paper trail. If there are specific patient characteristics that are going to affect their final outcome, it’s important to include them on the consent form and make sure that you document the discussion in the chart. Typically, I discuss the risk factors with the patient, document the conversation and add the patient-specific risk factors to the informed consent document along with my signature and their signature: The idea being that if someone were to review this document retrospectively, they’d be able to clearly see that the patient had a particular risk factor present, there was a discussion and education preoperatively about this condition, and the patient was made aware of the potential impact of this risk factor on their final outcome.

7 Discuss and document intraoperative changes. Intraoperative changes that seem to deviate from the original surgical plan are another common cause of lawsuits. Of course, you can and should make intraoperative changes on the fly; just be sure to explain them well to your patient postoperatively and document them accordingly. Have a conversation preoperatively with your patient about the surgical plan, with the caveat that adjustments may need to be made at the time of surgery. Typically, the possibility of intraoperative changes is also included in the written consent form.

8 Double check your data and measurements. Data transcription errors may occur between the clinic and the ASC. Implanting the wrong lens or the incorrect lens power is another common cause of lawsuits. Avoid this by double checking your measurements, having a consistent system in place and making sure lens verifications are made prior to implantation. It’s also good practice to ensure that your final operative report is not a generic template and accurately reflects each procedure.

9 Clearly document insurance billing and out-of-pocket fees. One universal source of patient discontent occurs when it’s unclear
Finally, an FDA-Approved Ophthalmic MMC.

**MITOSOLVED.™**

**UPGRADE YOUR STANDARD OF CARE**

- **NO REFRIGERATION** ¹
- **24 MONTH SHELF LIFE AT ROOM TEMPERATURE** ¹
- **USP <800> COMPLIANT** ²
- **FDA APPROVED FOR OPHTHALMOLOGY** ³

**Mitosol.com**
1-877-393-6486
(877-EYE-MITO)

---

2. USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings

US Pat #7,806,265, #8,186,511, D685,962, #9,205,075, #9,539,251, #9,649,428 Other US and International patents issued and/or pending

© Mobius Therapeutics, LLC 2021

**Mitosol®**
(mitomycin for solution)
0.2 mg/vial
Kit for Ophthalmic Use
THE TOTAL PACKAGE.
Mitosol® (mitomycin for solution) 0.2 mg/vial Kit for Ophthalmic Use. Rx only

**BRIEF SUMMARY:** Please consult package insert for full prescribing information.

**INDICATIONS AND USAGE:** Mitosol® is an antimetabolite indicated for use as an adjunct to ab externo glaucoma surgery.

**CONTRAINDICATIONS:** Hypersensitivity: Mitosol® is contraindicated in patients that have demonstrated a hypersensitivity to mitomycin in the past.

**WARNINGS AND PRECAUTIONS:** Cell Death: Mitomycin is cytoxic. Use of mitomycin in concentrations higher than 0.2 mg/mL or use for longer than 2 minutes may lead to unintended corneal and/or scleral damage including thinning or perforation. Direct contact with the corneal endothelium will result in cell death. Hypotony: The use of mitomycin has been associated with an increased incidence of post-operative hypotony. Cataract Formation: Use in phakic patients has been correlated to a higher incidence of lenticonal change and cataract formation.

**EMBRYO FETAL TOXICITY:** Can cause fetal harm. Advise of potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to use.

**ADVERSE REACTIONS:** Ophthalmic Adverse Reactions: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most frequent adverse reactions to Mitosol® occur locally, as an extension of the pharmacological activity of the drug. These reactions include: Blebitis: bleb ulceration, chronic bleb leak, encapsulated cystic bleb, bleb-related infection, wound dehiscence, conjunctival necrosis, thin-walled bleb. Cornea: corneal endothelial damage, epithelial defect, anterior synechia, superficial punctuate keratitis, Descemet's detachment, induced astigmatism. Endophthalmitis; Hypotony: choroidal reactions (choroidal detachment, choroidal effusion, serous choroidal detachment, supachoroidal hemorrhage, hypotony maculopathy, presence of suprachoroidal fluid, hypooechogenic suprachoroidal effusion); Inflammation: iritis, fibrin reaction; Lens: cataract development, cataract progression, capsule opacification, capsular contraction and/or capsulotomy rupture, posterior synechia; Retina: retinal pigment epithelial tear, retinal detachment (serous and rhegmatogenous); Scleritis: wound dehiscence; Vascular: hyphema, central retinal vein occlusion, hemiretinal vein occlusion, retinal hemorrhage, vitreal hemorrhage and blood clot, subconjunctival hemorrhage, disk hemorrhage; Additional Reactions: macular edema, sclera thinning or ulceration, intracranial lens capture, disk swelling, malignant glaucoma, lacrimal drainage system obstruction, ciliary block, corneal vascularization, visual acuity decrease, cystic conjunctival degeneration, upper eyelid retraction, dislocated implants, severe loss of vision.

**USE IN SPECIFIC POPULATIONS:** Pregnancy: Risk Summary: Based on findings in animals and mechanism of action, Mitosol® can cause fetal harm when administered to a pregnant woman. There are no available data on Mitosol® use in pregnant women to inform the drug-associated risk. In animal reproduction studies, parenteral administration of mitomycin resulted in teratogenicity. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Data: Animal Data-Parenteral administration of mitomycin in animal reproduction studies produced fetal malformations and embryofetal lethality. Lactation: Risk Summary: There are no data on the presence of mitomycin in human milk, the effects on the breastfed child, or the, effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during and for 1 week following administration of Mitosol®.

**FEMALES AND MALES OF REPRODUCTIVE POTENTIAL:** Mitosol® can cause fetal harm when administered to pregnant women. Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to using Mitosol®. Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

---

**REFRACTIVE/CATARACT RUNDOWN | Expert Witness**

how a premium IOL procedure is billed. Providing the patient with clear information regarding fee breakthrough preoperatively is key to mitigating this risk. Maintain a copy in the chart and be sure it clearly states what the patient has already paid or might still need to pay.

10 Promptly disclose and address complications and postoperative sequelae. Patients understand that complications can occur, but what makes most people upset is when communication is poor and they feel that things have been hidden from them, and believe they’ve been abandoned.

The first step is to ensure you’ve had a thorough preoperative discussion about the risks and potential complications of the surgery. When postoperative complications occur, your communication skills and ability to deliver bad news will be key. Speak with compassion, empathy and honesty.

Take your next steps promptly, whether that’s repeat testing or referral, and monitor progress closely. Be open to getting a second opinion or additional help from specialists when necessary and without delay.

11 Be available to your patients. You never want your patient to feel abandoned by you. While it’s natural to want to avoid discussing unpleasant situations such as complications, it’s important to remain accessible to your patients. Even if they’re stable and you may not need to see them for three weeks, these patients may require extra reassurance that only a visit with you can provide. Think of more visits as opportunities for patient education and relationship-building.

Keeping these pearls in mind will help give you an opportunity to focus on good patient care and decrease your risk for litigation.

To paraphrase a Walt Disney movie, “It’s a tale as old as time”: The younger generation doesn’t work as hard, doesn’t understand adversity and is spoiled. If that were consistently true, generation after generation, then our forefathers were lucky to have survived to adulthood. And ‘kids nowadays’ wouldn’t lift a finger without complaining—and they do complain. They’d never be able to “walk to school uphill, both ways, in the snow” like we had to. The apocryphal Millennials of our time—those born between 1981 and 1996—have had a lot written about them and have generated enough cliches that all you have to do is say the word “Millennials,” roll your eyes and give a deep sigh to write off an entire generation. But is that an even remotely deserved approbation?

Well, as uncomfortable as it may be to say, there’s a kernel of truth to most stereotypes. But how much of that is really the fault of the individuals in this demographic vs. the society in which we now live? If Millennials are thought to be lazy, irresponsible and spoiled, how much of that, if true, has been facilitated by how life has changed? We’ve become a society where you don’t have to expend as much physical energy to earn a living. Remote work, automation, computers, online shopping and everything else you could potentially want are at your fingertips. If you take advantage of that, is it being lazy or just living in the 2020s? If we’re trying to be more attuned to the challenges of living day-to-day, is that desirable or just coddling? It’s difficult to know.

In my role as attending surgeon at the hospital and an operations consultant for the resident clinics and comprehensive practices, I interact with the younger generation—residents, fellows and new associates—every day. As a result, I’m constantly reminded that the world has changed. I suppose it’s natural that I view my daily interactions through the lens of my experience, but I’m afraid I’ve fallen into the habit of using my approach to work/life as a benchmark for all those who have followed. I often shake my head at attitudes and behaviors I can’t understand.

Well, as uncomfortable as it may be to say, there’s a kernel of truth to most stereotypes. But how much of that is really the fault of the individuals in this demographic vs. the society in which we now live? If Millennials are thought to be lazy, irresponsible and spoiled, how much of that, if true, has been facilitated by how life has changed? We’ve become a society where you don’t have to expend as much physical energy to earn a living. Remote work, automation, computers, online shopping and everything else you could potentially want are at your fingertips. If you take advantage of that, is it being lazy or just living in the 2020s? If we’re trying to be more attuned to the challenges of living day-to-day, is that desirable or just coddling? It’s difficult to know.

In my role as attending surgeon at the hospital and an operations consultant for the resident clinics and comprehensive practices, I interact with the younger generation—residents, fellows and new associates—every day. As a result, I’m constantly reminded that the world has changed. I suppose it’s natural that I view my daily interactions through the lens of my experience, but I’m afraid I’ve fallen into the habit of using my approach to work/life as a benchmark for all those who have followed. I often shake my head at attitudes and behaviors I can’t understand.

It seems so different from when I was a resident and new attending. There are so many small examples from our world: not showing up for lectures; complaining about having to work up their own patients; unhappy that clinics are running past 4 p.m.; having to see too many patients; or having to change their plans at the last minute to help out. In the ‘days of the giants,’ we had to admit every patient for surgery, clinics regularly ran until 6 p.m., and there was no ‘night float’ to give you a day off after taking call—just to name a few adversities we had to deal with.

In medicine there used to be a more widely accepted dedication to work, no matter how all-consuming it was. It was part education and part a rite of passage. Home life was secondary. Sleep was secondary. Even happiness was secondary, unless you could derive it from being on-call and working the entire next day.

The watershed moment when this all began to change was the death of a patient in New York City in 1984 under the care of a medical intern who’d been up all night and working the next day. As it happened, the patient was the daughter of a New York Times reporter, and the incident created such a firestorm that national resident training rules were totally rewritten. It sparked an ongoing discussion of work/life balance not only for the benefit of patients, but for the residents themselves.

While there were necessary changes, expectations for commitment to work have also changed. What was the norm 30 years ago isn’t accepted now. This also altered what doctors expected when they went out into the workforce. So, whether members of this generation are less inclined to devote themselves to their careers, or society is moving toward a more holistic balance between work and life, the result is both a shortage of health-care providers and a disconnect between those just beginning their careers and those of us at the end. Should I be proud of the hills I had to climb (each way) or welcoming of a better quality of life? Well, at least now there’s less snow.
LIRIC: A Novel LVC Treatment

This non-invasive method of correcting refractive error alters the cornea’s index of refraction rather than its shape.

After almost two decades in the works at the University of Rochester, a new vision-correction technology called LIRIC, or laser-induced refractive index change, was successfully used in its first in-human trial to correct refractive error non-invasively. The procedure operates at pulse energies much lower than what’s currently used in femto-LASIK, making it a fundamentally safer procedure, according to LIRIC pioneer Scott MacRae, MD, chief of the Cornea and Refractive Surgery Service and a professor of ophthalmology and visual sciences at the Flaum Eye Institute, University of Rochester.

Here, Dr. MacRae explains how this new technology works, and shares some results of the trial.

Stromal Modification

LIRIC uses pulse energies 100 to 1,000 times lower than the flap-cutting regime. “Without tissue ablation, there’s no incision, less keratocyte cell death and less nerve death in the cornea,” Dr. MacRae explains.

“The corneal stroma can be thought of as a mixture of constituent ingredients, namely collagen and water,” he says. “Collagen (dehydrated) has an index of refraction of about 1.5; water is 1.33. In a healthy cornea, water content is finely controlled by the endothelial pump and proteoglycans of the stroma, resulting in a stromal index of roughly 1.38. LIRIC’s mechanism is based on modifying this mixture of collagen and water within a micrometer-sized region of action.”

“Within the focal spot of the femtosecond laser, the collagen matrix is modified, and the collagen fibrils are more densely packed, leading to a change in the refractive index,” he continues. “The magnitude of LIRIC is proportional to the pulse energy (again, below the damage threshold) and the spot is scanned across the optical zone. Thus, a variety of optical wavefronts can be inscribed within the cornea (e.g., sphere, cylinder, higher-order aberrations, multifocal, etc.).”

Dr. MacRae says LIRIC’s greatest advantage is its non-invasive nature. By avoiding ablation, LIRIC preserves the cornea’s original curvature.

**CORNEAL THICKNESS:**

<table>
<thead>
<tr>
<th>Average Change:</th>
<th>-11 ± 10µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>&lt;0.05, paired Student’s t-test</td>
</tr>
<tr>
<td>Measured with placido corneal topographer (Galilei, Ziemer)</td>
<td></td>
</tr>
</tbody>
</table>

**ENDOTHELIAL CELL COUNT:**

<table>
<thead>
<tr>
<th>Average Change:</th>
<th>-2.8 ± 5.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>=0.12, paired Student’s t-test</td>
</tr>
<tr>
<td>Measured with specular microscope (Nidek)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1A. A LIRIC-treated eye one day postop. Patients typically recover in 24 hours due to the non-invasive and non-ablative nature of LIRIC.
and avoids epithelial remodeling and the subsequent regression seen in the early days of laser refractive surgery, he points out.

“The lower pulse energies have also been shown, histologically, to preserve the stromal nerves (unlike laser refractive surgery),” he notes. “We expect this will reduce the rates of postop dry eye, but this remains to be seen. Also, LIRIC doesn’t remove tissue, obviating the concern about corneal ectasia. Subjectively, this incision-free procedure may attract patients for whom ‘fear of surgery’ is a major obstacle to getting laser vision correction. Incisionless vision correction also may have implications for in-office procedures and applicability to the developing world.”

The Procedure
The LIRIC platform can correct sphere, cylinder, higher-order aberrations and even presbyopia using multifocal patterns. Dr. MacRae says that good candidates include those who are unable to undergo LASIK due to a thin cornea and those who fear invasive surgery.

“We’re also developing LIRIC for use as a postop touch-up in intraocular lenses and contact lenses,” he says. “The IOL touch-up is important for post-surgery residual refractive error. Contact lenses are exciting because we can offer popular diffractive multifocal patterns that are successful for cataract patients in the form of a contact lens for phakic presbyopes.”

He says that patients recover from LIRIC in about 24 hours. Additionally, since the corneal epithelium and stroma aren’t significantly disrupted, the patient doesn’t need to take topical antibiotics or steroids for the typical five to seven days, as in the current regimen with corneal refractive surgery.

Currently, the cornea procedure takes just under 90 seconds, but Dr. MacRae says the goal is much shorter. “We’re refining our laser system to meet a goal of less than 20 seconds per procedure,” he says. “For perspective, the first LIRIC contact lenses we produced took more than 10 hours to write in hydrogel materials. These first lenses were so-called ‘hero experiments’ run by graduate students at the University of Rochester.”

Dr. MacRae adds that because LIRIC is less disruptive and doesn’t thin the cornea, it has the potential to be used for repeat treatments if a patient’s refractive error changes or the patient later develops presbyopia. “We’ve done repeated treatments in animals, but this needs to be validated in human studies,” he says.

How easily will refractive surgeons be able to adopt and offer LIRIC in the future? “LIRIC certainly requires a laser system specialized for modifying refractive index,” Dr. MacRae says. “At the moment, the LIRIC device is a stand-alone system (Clerio Vision). In the future,

(Continued on p. 27)
• Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments.

WARNINGS AND PRECAUTIONS
• 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.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
• Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA.

ADVERSE REACTIONS
• 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.

SERIOUS ADVERSE EVENTS
• Serious adverse events related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA, including endophthalmitis and retinal detachment.

PROPER ASEPTIC TECHNIQUE
• 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
• Intraocular inflammation has been reported with the use of EYLEA.

SUSTAINED INCREASES IN INTRAOCULAR PRESSURE
• Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors.

ATREAS
• Arterial thromboembolic events (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).


REFERENCES

2. ELYA is a registered trademark of Regeneron Pharmaceuticals, Inc.

© 2021, Regeneron Pharmaceuticals, Inc. All rights reserved. 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

<table>
<thead>
<tr>
<th></th>
<th>VIEW 1</th>
<th>VIEW 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EYLEA Q4</td>
<td>95% (12.5 injections1)</td>
<td>95% (12.6 injections1)</td>
</tr>
<tr>
<td>EYLEA Q8‡</td>
<td>94% (7.5 injections1)</td>
<td>95% (7.7 injections1)</td>
</tr>
<tr>
<td>ranibizumab Q4</td>
<td>94% (12.1 injections1)</td>
<td>95% (12.7 injections1)</td>
</tr>
</tbody>
</table>

Primary Endpoint (Year 1)

Vision was maintained at Year 1 with ≈5 fewer injections with EYLEA Q8 vs ranibizumab Q4

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

ADVERSE REACTIONS

• Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

• The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

• Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

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


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

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

- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Retinal Venous Occlusion (RVO)
- Polypoidal Choroidal Vasculopathy
- Dry Age-Related Macular Degeneration
- Neovascular (Wet) Age-Related Macular Degeneration (AMD)

2. Indications and Usage

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

- Neovascular (Wet) Age-Related Macular Degeneration
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)

3. Contraindications

- Hypersensitivity
- Retinal tear
- Corneal edema
- Retinal pigment epithelium tear
- Detachment of the retinal pigment epithelium
- Ocular hyperemia
- Intraocular pressure increased
- Vitreous detachment
- Vision blurred
- Foreign body sensation in eyes
- Injection site pain
- Eyelid edema

4. Precautions

- Hypersensitivity
- Retinal tear
- Corneal edema
- Retinal pigment epithelium tear
- Detachment of the retinal pigment epithelium
- Ocular hyperemia

5. Warnings and Precautions

- Hypersensitivity
- Retinal tear
- Corneal edema
- Retinal pigment epithelium tear
- Detachment of the retinal pigment epithelium
- Ocular hyperemia

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EYLEA (N=1152)</th>
<th>Control (N=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hyperemia</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry eye</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>White blood cells</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Uveitis</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Retinal pigment epithelium tear</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Detachment of the retinal pigment epithelium</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EYLEA (N=287)</th>
<th>Control (N=578)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hyperemia</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry eye</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>White blood cells</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Uveitis</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Retinal pigment epithelium tear</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Detachment of the retinal pigment epithelium</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EYLEA (N=595)</th>
<th>Control (N=578)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hyperemia</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry eye</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>White blood cells</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Uveitis</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Retinal pigment epithelium tear</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Detachment of the retinal pigment epithelium</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data were not available in patients who had a previous exposure to EYLEA.

6.3 Clinical Trials Experience

In the wet AMD studies, the incidence of reported thromboembolic events in 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 approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

7.7 Pregnancy

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 ATEs was 2% (9 out of 378) 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 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.
LIRIC: A Novel LVC Treatment
(Continued from p. 23)

we may pursue coupling the LIRIC system with a flap-cutter to reduce the footprint in the OR, but that’s yet to be determined.”

Establishing Safety

The first in-human trial established the safety profile of LIRIC when performed using a blue, 405-nm wavelength laser system. “All 27 patients showed excellent safety outcomes,” Dr. MacRae says. “No eyes exhibited inflammation or a wound-healing response. All corneas were clear post-treatment and there were no signs of haze, scarring, endothelial damage or opacity.

“We were very pleased with these outcomes,” he says. “However, since before this we had only tested the procedure in anesthetized animal models, we weren’t sure what to expect regarding the patient’s reaction to the treatment. For example, would the laser be ‘too bright’? However, it turned out that the flat-applanation patient interface caused patients’ vision to fade after about five seconds with applanation, similar to flat-applanation for cutting a LASIK flap. This made the treatment virtually invisible.”

So far, in vivo animal experiments have demonstrated that LIRIC treatment persists in the cornea for up to two years post-treatment (the longest animals have been tracked to date).34 On-going research and clinical studies are being conducted to demonstrate the same in humans.

As for long-term consequences, Dr. MacRae says, “We have no reason to expect that altering the cornea’s refractive index will have any negative effects down the line. LIRIC operates at pulse energies much lower than what’s currently used in femto-LASIK, so it’s fundamentally a safer procedure. We’ve also found that LIRIC has had no detrimental effect on endothelial cell count, which is further evidence of safety.”

LIRIC’s Future

Dr. MacRae says that in addition to reducing the treatment time to under 20 seconds, they’re still investigating the best laser paradigm to use. “For example, there’s already ample precedent for using near-infrared femtosecond lasers for ablation (e.g., corneal flaps, SMILE, etc.); therefore, LIRIC may have broader acceptance if it’s performed with a more familiar laser wavelength. However, the physics of multiphoton absorption dictates that the longer the wavelength, the more challenging it is to produce the desired effect. More research is required before we finalize our decision on a wavelength and laser settings.”

A PARADIGM SHIFT IN REFRACTIVE SURGERY?

“A non-incisional and non-ablative refractive surgical procedure would represent a paradigm shift in how we perform refractive surgery,” notes Edward Manche, MD, a professor of ophthalmology and director of the Cornea and Refractive Surgery Service at Stanford University. “Of course ... it would need to achieve outcomes at least as good as what we can achieve with our current state-of-the-art LASIK, PRK and SMILE surgical procedures.”

He says such a non-ablative refractive procedure would have a number of significant advantages over current ablative procedures. “There would be little or no concern with regards to biomechanical weakening of the cornea and little or no risk of infectious keratitis or non-healing epithelial defects,” he says. “It could also be useful in very thin corneas and corneas with borderline corneal topographies. Additionally, the prospect of potentially minimizing postop dry eye, due to little or no effect on the corneal nerve plexus, is also appealing.

“LIRIC may prove to be especially useful in addressing residual refractive errors after cataract surgery,” he continues. “The LIRIC treatment could be performed on either the IOL or the cornea depending on the effectiveness of the different technologies. This would dramatically improve outcomes with cataract surgery and would also offer patients the ability to have multifocality on their IOL or cornea to reduce or eliminate the need for near-vision glasses after cataract surgery.”

He says safety is the most important issue to study when considering a novel technology. “There have been animal studies as well as studies in humans that assessed the safety of the procedure,” he says. “Based on the preliminary data presented at meetings, it appears that the procedure is safe. However, larger, longer-term, prospective, multicenter clinical trials are needed to establish the safety, efficacy, predictability and stability of the procedure before it can be widely adopted.

“LIRIC has the potential to displace LASIK, PRK and SMILE surgery as the dominant refractive surgical procedure,” he says. “In order to do so, LIRIC would have to have the same or superior safety, efficacy, predictability and long-term stability that’s seen with our current state-of-the-art keratorefractive surgeries. In the near term, it may be initially used to induce multifocality in the cornea or IOL to treat presbyopic and/or pseudophakic patients.”

—CL

DISCLOSURES

Dr. MacRae is a paid consultant to Clerio Vision, the company developing LIRIC. Dr. Manche has no financial disclosures related to LIRIC. He owns equity in RxSight, VacuSite and Placid0 and is a consultant to Avedro and Johnson & Johnson Surgical. He also conducts sponsored research for Allergan, Alcon, Avedra, Carl Zeiss Meditec, Novartis and Presbia.

PATIENT SELECTION: TRAB, XEN OR PRESERFLO?

Age, severity of disease and a host of other factors should be considered when choosing a procedure for a particular patient.

Trabeculectomy has been performed successfully for many years to reduce both intraocular pressure and the number of medications required to maintain a healthy pressure. Newer procedures, such as the Xen Glaucoma Treatment System (Abbvie/Allergan) and PreserFlo Ab-Externo MicroShunt (Santen), are also options for managing glaucoma, but patient selection is key. In this article, glaucoma specialists explain how they decide between the procedures.

According to Louis B. Cantor, MD, who is in practice in Indianapolis, there are very limited data to help surgeons make patient selection decisions. “Patient selection for not only these but our other MIGS procedures is still evolving rather rapidly and is often done without good evidence, simply because we don’t have a lot of good data. The limited studies we have are retrospective or case series,” he explains. “Part of the goal of the device-based procedures, such as Xen and PreserFlo, was to standardize trabeculectomy and to minimize some of the complications of a bleb-forming procedure. However, Xen has evolved to include many variations in technique. It was originally designed to be performed as an ab inteno procedure through clear cornea and injected translimally and subconjunctivally. But now, people are doing a lot of open conjunctival dissections, applying mitomycin in different ways and doing primary needling at the time of surgery to prevent or minimize the risk of tube occlusion, which is not an uncommon complication. PreserFlo is done using an external approach, so I think the techniques for doing it are more standardized. Trabeculectomy techniques can vary widely between surgeons. There are many individual techniques, and there is a lot of art to trabeculectomy,” Dr. Cantor explains.

Trabeculectomy

The effectiveness and safety profile of trabeculectomy are well-known, as it’s been a mainstay for surgeons who need a procedure that gives them a significant amount of pressure lowering and who are willing to go a more invasive route.

Data from the landmark Tube vs. Trabeculectomy study bear this out. In the trial, with follow-up at 17 clinical centers, 105 patients with a history of prior cataract extraction and/or failed filtering surgery underwent trabeculectomy with mitomycin C. They were evaluated for IOP, visual acuity, use of supplemental medical therapy and rate of failure. At five years postoperatively, their mean IOP was 12.6 ±5.9 mmHg, and they were on 1.2 ±1.5 glaucoma medications. The probability of failure during the five years of follow-up was 46.9 percent, and the rate of reoperation was 29 percent.1

Recently, researchers have taken a look at the results of these procedures in patients without a history of surgery, in the Primary Tube vs. Trabeculectomy study. As part of the study, 117 glaucoma patients underwent trabeculectomy with MMC. The researchers found that the cumulative probability of failure after three years was 28 percent in the trab group. Postop IOP was 12.1

This article has no commercial sponsorship.

Dr. Stiles has received research support from AqueSys, which was acquired by Allergan, and Santen. Dr. Cantor has consulted for Allergan and Santen. Dr. Lehrer has no financial interest in any of the products mentioned in the article.
±4.8 mmHg at three years, and the average number of postop glaucoma medications for patients in the trab group was 1.2 ±1.5. Serious complications requiring reoperation or producing a loss of two or more Snellen lines developed in nine trabeculectomy patients (8 percent).²

According to Michael Stiles, MD, who is in practice in Overland Park, Kansas, the lowest pressures can be obtained with a trabeculectomy. “In patients who need a super-low pressure with no medication dependence, I prefer trab. I use Xen for all other patients. It’s my go-to filtration procedure for most patients because, if it scars or if it doesn’t succeed, there’s still a lot of real estate left to do a trabeculectomy. In fact, another indication for a trabeculectomy is a failed Xen procedure. Many times, I’ll perform trabeculectomy prior to doing a traditional tube shunt,” he says.

Dr. Cantor agrees. “If you do a lot of trabeculectomy, I still feel that it’s the most effective procedure overall, and you can manage the safety concerns. You also don’t have that additional cost initially, because there’s no device to pay for. For those patients at highest risk of going blind, who have refractory glaucoma that’s failed other things, and for younger patients, I certainly lean toward trabeculectomy. And I strongly lean toward trabeculectomy in patients who have a high risk of significant loss of vision, loss of quality of life, or visual impairment during their lifetime because of where they are in the spectrum of their glaucoma,” he says.

Richard A. Lehrer, MD, who is in practice in Alliance, Ohio, also believes that trabeculectomy with mitomycin-C is best for achieving very low pressures. “If a patient needs single-digit pressures reliably, the best way to get there is with a trabeculectomy. However, if a patient needs pressures in the low teens, procedures like Xen and hopefully PreserFlo will be able to achieve that. The problem with Xen in my hands is that the success rate is significantly lower than with a trabeculectomy. I explain to patients that the risk of performing a Xen is lower than the risk of doing a trab, but the chance of failure is higher,” Dr. Lehrer explains.

If he only has one chance to achieve the necessary pressure, Dr. Lehrer will most likely choose a trab. “The Xen has a 25- to 30-percent rate of needling, and of those needlings, only about 50 percent are successful in my hands,” Dr. Lehrer adds.

**Xen**

The Xen gel stent is a 6-mm hydrophilic flexible tube with a 45-µm lumen. It is made of porcine collagen-derived gelatin cross-linked with glutaraldehyde, which is non-inflammatory and causes minimal extracocular fibrotic or vascular response to the implant material. The Xen decreases IOP by creating a permanent drainage shunt from the anterior chamber to the subconjunctival space through a scleral channel.

The design of the Xen stent is based on the principles of laminar fluid dynamics. The Hagen-Poisson equation was used to calculate the required internal dimensions of a tube that would prevent hypotony at an average aqueous humor production of 2 to 3 μL/min, and would provide a steady-state IOP floor of approximately 6 to 8 mmHg.

The FDA approved Xen in 2016 for use in POAG and pseudoexfoliative or pigmentary glaucoma in eyes with open angles that are unresponsive to maximum tolerated medical therapy.

“All-in-all, what I like about the Xen, especially with an ab interno approach, is that about 50 percent of the time you can achieve a very good long-term IOP with a quick procedure. With a trab, the healing time is longer, and the chance of early and late complications is probably a little bit higher,” Dr. Lehrer says.

Dr. Cantor adds that it can be worthwhile to consider Xen or PreserFlo in patients who are refractory to medications and laser who don’t have advanced glaucoma. “Maybe we’ve even done a MIGS procedure, such as a canal-based procedure, and we’re still not controlling pressure adequately, and the patient can’t use or can’t tolerate medications or the medications are not effective. We may not want to put that patient in the position of having a trabeculectomy at their stage of disease or at their age, so it’s worthwhile to consider Xen or PreserFlo,” he says.

According to Dr. Cantor, some surgeons suggest that Xen and PreserFlo may be contraindicated in patients with a history of angle-closure glaucoma. “You need to have somewhere to place the tube in the eye that isn’t too close to the cornea. In those eyes, you can often do a trabeculectomy because you’re doing an iridectomy. With time, we’re going to learn where these procedures work best and don’t work relative to each other. But currently, we don’t have a lot to go on other than personal experience and limited data,” he says.

**PreserFlo**

The PreserFlo, which is currently pending Food and Drug Admin-
istration approval, is composed of poly(styrene-block-isobutylene-block-styrene), which is biologically inert and has been used in coronary stents. The properties of this material are expected to decrease the risk of postoperative epithelial scarring and fibrosis, which are often causes of surgical failure after glaucoma filtering procedures.

The design of the device is based on assumptions of the Hagen-Poiseuille equation for prediction of pressure. The device’s maker says that as long as aqueous production is 2 µL/min or more, postoperative intraocular pressure should be maintained above 5 mmHg. When positioned properly, the distal end of the MicroShunt should filter aqueous to the subconjunctival and sub-Tenon’s space 6 mm posterior to the limbus, allowing for posteriorly directed flow and bleb formation.

This device looks promising. In fact, a recent study found that PreserFlo MicroShunt and Xen Gel Stent implantations achieved comparable results in primary open-angle glaucoma in terms of IOP-lowering and surgical success, with a similarly high safety profile.2

This was a retrospective, comparative case series of primary open-angle glaucoma patients with at least six months of follow-up after a MicroShunt or Xen implantation augmented with mitomycin C. (In terms of disclosures, one of the researchers received research grant support from Santen, one was an Allergan consultant and another was a consultant for Santen.)

Forty-one eyes of 31 patients underwent Xen implantation, and 41 eyes of 33 patients underwent PreserFlo MicroShunt implantation. Baseline characteristics were similar, except for more combined surgeries with phacoemulsification in the Xen group (37 percent) compared with the PreserFlo group (2 percent). Mean baseline IOP ± standard deviation decreased from 19.2 ±4.4 to 13.8 ±3.8 mmHg (n=26) in the Xen group and from 20.1 ±5.0 to 12.1 ±3.5 (n=14) in the PreserFlo MicroShunt group at 24 months of follow-up. Additionally, the number of IOP-lowering medications dropped from 2.5± 1.4 to 0.9± 1.2 in the Xen group and from 2.3± 1.5 to 0.7± 1.1 in the PreserFlo MicroShunt group. The researchers determined that the probability of successful ac-

The hope with PreserFlo is that surgeons will be able to achieve lower long-term pressure with less medication dependence than Xen and avoid the first week of hypotony. “It also has advantages over trabeculectomy: it trabeculectomy requires many postop visits in which you are manipulating outflow by cutting or removing flap sutures to avoid failure and hypotony at the same time,” Dr. Stiles says. “There’s just a lot of postop care involved, and not all patients can make it to the office six or eight times within the first six weeks to monitor progress. Both Xen and PreserFlo have this advantage over trabeculectomy; however, I’m more likely to have episcleral fibrosis issues with Xen compared to trab, and there’s more need for some medication dependence. I’m hoping PreserFlo is an improvement upon that, but time will tell.”

Suggested Reading


According to Dr. Stiles, experience overseas suggests that PreserFlo may achieve lower intraocular pressures than Xen. “PreserFlo may be another alternative if you’re trying to avoid a trabeculectomy in patients who need a low pressure,” he says. “I do see some early hypotony the first week with the Xen because there can be some flow around the tube. In comparison, the PreserFlo device fits into a snug pocket. I tend to avoid Xen procedures in certain patients with high opening pressures and in those at risk for choroidal hemorrhage that can occur with early hypotony.”

Bleb-associated infection, or “blebitis” after a trabeculectomy.
OPEN YOUR EYES TO

DISCOVER EXCLUSIVE ACCESS TO ALL THINGS REFRESH®

Our full-service, dedicated team is here to assist you and your staff with all your REFRESH® needs.

Call us and see how REFRESH® Concierge can help you bring relief to your patients.

833-REF-SMPL  7:30 a.m.–7 p.m. CT, M–F

©2021 AbbVie. All rights reserved. All trademarks are the property of their respective owners. REF138377 07/20
Accurately evaluating a patient’s status and the risk that the disease will get worse is critical to choosing the most appropriate treatment.

When faced with treating a new glaucoma patient, there are two important predictors of patient outcomes to consider. First, one must determine the stage of disease—i.e., how advanced the patient’s disease is at the time of presentation. Second, one needs to determine the patient’s risk of progression. These are two of the primary determinants of the type and extent of treatment we offer.

Staging the Disease

There are two reasons it’s important to accurately stage the disease. First, as already noted, accurately staging the disease informs the type of clinical care we provide, as described in the American Academy of Ophthalmology’s Preferred Practice Patterns. In particular, advanced disease in a presenting patient should impact our choice of treatment because of what we learned from the CIGTS (Combined Initial Glaucoma Treatment Study) trial, led by Paul Lichter, MD. That study showed that late-stage glaucoma patients do better over the long term (in terms of visual field preservation) if they have a trabeculectomy as their initial treatment. Thus, when we encounter a patient with advanced disease, we’re justified in considering an aggressive initial treatment such as trabeculectomy.

The second reason it’s important to accurately stage the disease is that there are billing and coding ramifications. If your patient’s glaucoma is mild or moderate, a MIGS procedure is reimbursable; in contrast, if the glaucoma is severe, a MIGS procedure won’t be reimbursed. Similarly, OCT nerve fiber layer testing isn’t reimbursable if your patient has severe stage-three glaucoma. So staging the disease correctly is important if you hope to get reimbursed for any procedures you perform.

Medicare defines three stages of glaucoma. However, it’s important to remember that this staging isn’t based on findings from any specific clinical trial. (While billing and coding should comply with Medicare definitions in order to obtain proper reimbursement, our clinical decisions should be informed by data and definitions from the landmark clinical trials, in order to achieve the best outcomes.)

For coding purposes, H40.1131 is used for early or mild-stage glaucoma. This is defined as optic nerve abnormalities consistent with glaucoma, and retinal nerve fiber layer changes, but with no visual field abnormalities. (The exception would be abnormalities only present on SWAP or FTD visual field testing.)

H40.1132 is used for moderate-stage glaucoma. Medicare defines that as optic nerve abnormalities consistent with glaucoma and retinal nerve fiber layer changes, plus visual field abnormalities in one hemi-field—but not within 5 degrees of fixation.

H40.1133 is used for advanced/severe-stage glaucoma, defined as optic nerve abnormalities consis-
tent with glaucoma, retinal nerve fiber layer changes, glaucomatous visual field abnormalities in both hemifields and/or vision loss within 5 degrees of fixation in at least one hemifield. The difference between these definitions and clinical-trial-based definitions can be seen by considering how advanced disease is defined in the CIGTS study; having a mean deviation greater than -10 dB on a visual field.

**Glaucocma Pathophysiology**

To understand the staging of glaucoma, it helps to review the pathophysiology of the disease. Glaucoma can be defined as a pathologic condition in which there’s a progressive loss of ganglion cell axons leading to visual field deficits, with elevated intraocular pressure as a known major risk factor.

We know that the primary damage occurs at the lamina cribrosa. What we don’t know for certain is exactly how this damage occurs. Both structural and vascular damage are seen as the disease progresses, and it’s not yet clear which one comes first. That’s led to two possible explanations for the development of the damage: the mechanical theory and the vascular theory.

Because the entry point of the ganglion cell axons at the lamina cribrosa is the structural weak point of the eye, the mechanical theory proposes that barotrauma resulting from the increased intraocular pressure found in glaucoma squashes the lamina, with both compressive and shearing forces causing damage. Because the ganglion cell axons pass through the laminar plates, they get stretched as the laminar plates are pulled apart.

To put it another way, the physiologic consequence of elevated IOP is inhibition of axoplasmic flow at the lamina cribrosa; the functional consequence of axonal loss (or dysfunction) is decreased sensitivity to light. It’s postulated that this damage then leads to diminished vascularization of this area; when tissue is dying, the body will be conservative and not send new blood vessels there. This theory has been suggested by Harry Quigley, MD, Jost B. Jonas, MD, and Douglas Anderson, MD.¹ ²

The vascular theory, favored by Jack Cioffi, MD,³ suggests that the vascular damage comes first, triggering the structural damage. This theory suggests that vascular dysfunction is caused by either the capillaries in the laminar cribrosa area losing some of their ability to autoregulate, or a problem with the glial cells that support the vessels, the pericytes. Pericyte loss then leads to an infarction. If this theory is correct, then this infarction leads to loss of tissue and the collapse of the lamina.

At this point, we don’t know whether the mechanical or vascular theory is correct. It’s most likely that the damage caused by glaucoma is multifactorial; in fact, both theories may be correct.

One way to look at glaucomatous disease is as an acceleration of the natural aging process, a process that leads to a loss of vision over time. A healthy eye experiences a loss of about 0.5 percent of ganglion cell axons per year as we age, as shown in research done by Rosario Hernandez-Neufeld, DDS. That’s one of the reasons that, even if there’s no disease present, you find decreased contrast sensitivity, reduced levels of spatial recognition and challenges with light-to-dark and dark-to-light adaptation as we age. This is one reason that older people don’t see as well as they did when younger, even if they’re considered healthy. Glaucoma, we believe, causes a hyper-acceleration of that aging process in patients with the disease.

**Determining Extent of Damage**

To stage the disease, in addition to a thorough physical exam of the patient’s eyes, we have to evaluate the patient’s condition using the best tools at our disposal. For most clinicians today, that means obtaining objective structural data by scanning the retina and optic nerve using optical coherence tomography, as well as performing visual fields to get a more subjective measure of visual performance. As most opththalmologists know, structural and functional testing—the former objective and the latter subjective—often don’t agree regarding the patient’s condition.

The earliest that standard visual field testing can pick up glaucomatous damage is when there’s a 30- to 45-percent loss of ganglion cells. This was verified in two key studies. The first was a study conducted by Harry Quigley, MD, that looked at

---

**PREDICTIVE RISK FACTORS ASSOCIATED WITH GLAUCOMA PROGRESSION**

<table>
<thead>
<tr>
<th>Risk factor for progression</th>
<th>Risk factor for blindness</th>
<th>Risk factor in every major study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced disease at time of presentation</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Elevated intraocular pressure</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Diurnal IOP fluctuations</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Older age</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Central Corneal Thickness</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Disc hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large beta zone of peripapillary atrophy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although numerous risk factors have been found to be associated with glaucoma progression in different studies, only one has been associated with progression in every major clinical trial: advanced disease at the time of presentation.
glaucoma stage is related to abnormality in visual field.

The European Glaucoma Prevention Study and OHTS study made it clear that we often pick up structural optic nerve or nerve fiber layer damage earlier than visual field loss. In the OHTS study, 50 percent of patients progression was detected by structural optic nerve criteria; in the EGPS study, it was 40 percent. However, it must be noted that even though 50 percent progressed by optic nerve criteria before the visual field revealed the loss in the OHTS study, the visual field picked up the problem first in the other 50 percent of patients.

From a practical perspective, this means that if you note a visual field change that’s highly suggestive of glaucoma—specifically, a visual field defect that localizes to the retinal nerve fiber layer—then treatment is indicated. Glaucoma doesn’t always present with anatomical changes on structural imaging; the visual field can sometimes be the first indication of pathology. (This ties into the evolving concept called “green disease,” where even though a patient’s “normal/abnormal” OCT chart shows all green—suggesting that the readings are all within the normal range—the patient actually does have glaucomatous disease. You may find the evidence on visual field testing, or in other evidence picked up by OCT, such as nerve fiber layer thinning and/or asymmetry over time.)

**Risk Factors for Progression**

Risk factors for progression are another important determinant when evaluating a patient for glaucoma. They allow us to approximate the likelihood that the patient’s vision will deteriorate in the near future (and long-term). Obviously, our treatment plan will be different when a patient has multiple risk factors for progression, as opposed to the patient having only one or two risk factors.

Different clinical studies have helped us identify numerous risk factors for glaucoma progression, including elevated IOP, significant diurnal IOP fluctuations, older age, reduced central corneal thickness, the presence of disc hemorrhages, certain genetic factors (for example, mutations in the myocilin, WDR-36 or OPTN genes, or single-nucleotide polymorphisms in the myocilin gene promoter), and a large beta zone of peripapillary atrophy. However, only one risk factor has been found to be statistically significant in every study: advanced disease at the time of presentation. It’s also one of three risk factors associated with glaucoma-related blindness, along with elevated IOP and significant diurnal IOP fluctuations. Even family history hasn’t been a significant predictor of progression in every study; it wasn’t a significant risk factor in the Ocular Hypertension Treatment Study, for example.

It’s not obvious why the other risk factors don’t have a significant association with progression in every study. However, it’s easy to guess why advanced disease consistently turns up as a powerful risk factor; once the disease is advanced, the tissue is already badly compromised. This damaged tissue is highly vulnerable to additional barotrauma. Ironically, if our treatments for glaucoma were more reliable and effective—if we were able to halt the disease no matter what stage it’s at—then advanced stage of disease wouldn’t be such a powerful risk factor.

In terms of stratifying risk, data from the Ocular Hypertension Treatment Study, led by Michael Kass, MD, at Washington University School of Medicine in St. Louis, has led to the so-called “rule of five.” The study found that you’re at high risk of developing glaucomatous disease within a five-to-10-year period if you have any or all of these factors: a cup-to-disc ratio greater than 0.5; central corneal thickness thinner than 555 µm; and/or an IOP higher than 25 mmHg—even if there’s no evidence of disease. There’s also an online risk calculator developed by the ocular hypertension treatment group (ohts.wustl.edu/risk/) that was verified by Felipe Medeiros, MD.

While the practicality of providing patients with a specific risk-of-glaucoma number using the calculator is...
The pinnacle of refractive performance.

Our greatest achievement yet, Contoura™ Vision outperformed even glasses and contacts.*1

With the exceptional results for improvement in UCVA, BSCVA and visual disturbances, Contoura™ Vision Topography-Guided LASIK has taken refractive outcomes even higher.1 By enhancing the symmetry of the corneal surface, Contoura™ Vision stands alone in refractive precision — and it’s only from WaveLight®.

For additional information or to schedule a demonstration, contact your Alcon sales representative.

For important safety information about this product, please refer to the adjacent page.

*Post hoc analysis of postoperative UCVA compared to preoperative BSCVA of 230 eyes contained in the FDA T-CAT pivotal trial at 12 months. The primary end point evaluated changes in BSCVA.
1. Results from FDA T-CAT-001 clinical study for Topography-Guided vision correction (with the 400 Hz ALLEGRO WAVE® Eye-Q Excimer Laser).
In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of myopia of up to +6.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D, or the reduction or elimination of myopia of up to +7.00 D at the spectacle plane and the wavefront-guided reduction or elimination of myopia of up to +8.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D.

In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of myopia of up to +6.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D, or the reduction or elimination of myopia of up to +7.00 D at the spectacle plane and the wavefront-guided reduction or elimination of myopia of up to +8.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D.

In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of myopia of up to +6.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D, or the reduction or elimination of myopia of up to +7.00 D at the spectacle plane and the wavefront-guided reduction or elimination of myopia of up to +8.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D.

In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of myopia of up to +6.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D, or the reduction or elimination of myopia of up to +7.00 D at the spectacle plane and the wavefront-guided reduction or elimination of myopia of up to +8.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D.

In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of myopia of up to +6.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D, or the reduction or elimination of myopia of up to +7.00 D at the spectacle plane and the wavefront-guided reduction or elimination of myopia of up to +8.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D.

In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of myopia of up to +6.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D, or the reduction or elimination of myopia of up to +7.00 D at the spectacle plane and the wavefront-guided reduction or elimination of myopia of up to +8.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D.

In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of myopia of up to +6.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D, or the reduction or elimination of myopia of up to +7.00 D at the spectacle plane and the wavefront-guided reduction or elimination of myopia of up to +8.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D.

In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of myopia of up to +6.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D, or the reduction or elimination of myopia of up to +7.00 D at the spectacle plane and the wavefront-guided reduction or elimination of myopia of up to +8.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D.

In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of myopia of up to +6.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D, or the reduction or elimination of myopia of up to +7.00 D at the spectacle plane and the wavefront-guided reduction or elimination of myopia of up to +8.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of +6.00 D.
debatable, it remains true that the “rule of five” risk factors play a crucial role in clinical decision-making when managing patients with ocular hypertension.

Imperfect, But Effective
To provide our patients with the most appropriate and effective care, we have to be able to evaluate their current and projected future status, as it relates to their glaucomatous disease, and we have to do so as accurately as possible. Our current tools and understanding are imperfect, but by applying them effectively to our clinical decision-making, we’ve made great strides in preserving vision for our patients.

Dr. Rhee is chair of the Department of Ophthalmology and Visual Sciences at University Hospitals Cleveland Medical Center; director of the Eye Institute at University Hospitals; division chief of ophthalmology at University Hospitals Ahuja Medical Center; and a professor at the Case Western Reserve University School of Medicine. Dr. Sozeri is an assistant professor of ophthalmology at Case Western Reserve University and University Hospitals. She’s a member of the glaucoma service and the associate glaucoma fellowship director. Dr. Lau is the 2021-2022 Case Western Reserve University and University Hospitals glaucoma fellow.

Cover Story GLAUCOMA STAGING AND RISK FACTORS

Imperfect, But Effective
To provide our patients with the most appropriate and effective care, we have to be able to evaluate their current and projected future status, as it relates to their glaucomatous disease, and we have to do so as accurately as possible. Our current tools and understanding are imperfect, but by applying them effectively to our clinical decision-making, we’ve made great strides in preserving vision for our patients.

Dr. Rhee is chair of the Department of Ophthalmology and Visual Sciences at University Hospitals Cleveland Medical Center; director of the Eye Institute at University Hospitals; division chief of ophthalmology at University Hospitals Ahuja Medical Center; and a professor at the Case Western Reserve University School of Medicine. Dr. Sozeri is an assistant professor of ophthalmology at Case Western Reserve University and University Hospitals. She’s a member of the glaucoma service and the associate glaucoma fellowship director. Dr. Lau is the 2021-2022 Case Western Reserve University and University Hospitals glaucoma fellow.

Imperfect, But Effective
To provide our patients with the most appropriate and effective care, we have to be able to evaluate their current and projected future status, as it relates to their glaucomatous disease, and we have to do so as accurately as possible. Our current tools and understanding are imperfect, but by applying them effectively to our clinical decision-making, we’ve made great strides in preserving vision for our patients.

Dr. Rhee is chair of the Department of Ophthalmology and Visual Sciences at University Hospitals Cleveland Medical Center; director of the Eye Institute at University Hospitals; division chief of ophthalmology at University Hospitals Ahuja Medical Center; and a professor at the Case Western Reserve University School of Medicine. Dr. Sozeri is an assistant professor of ophthalmology at Case Western Reserve University and University Hospitals. She’s a member of the glaucoma service and the associate glaucoma fellowship director. Dr. Lau is the 2021-2022 Case Western Reserve University and University Hospitals glaucoma fellow.

Imperfect, But Effective
To provide our patients with the most appropriate and effective care, we have to be able to evaluate their current and projected future status, as it relates to their glaucomatous disease, and we have to do so as accurately as possible. Our current tools and understanding are imperfect, but by applying them effectively to our clinical decision-making, we’ve made great strides in preserving vision for our patients.
The number of therapies being developed to treat this common ailment continues to grow.

Since dry eye is a common ophthalmic complaint, it’s been a popular target for drug and even device makers in recent years. Currently, many companies are working to develop additional therapeutic agents to treat this population, with many of these agents having unique and novel mechanisms of action. Here are some products you may have the option of incorporating into the dry-eye treatment protocol at your practice in the coming months or years.

Reproxalap (Aldeyra)
Aldeyra has been investigating a novel agent for the treatment of dry eye, reproxalap, which is a small-molecule reactive aldehyde species (RASP) inhibitor. The drug fights ocular inflammation and improves dry-eye symptoms through a unique mechanism of action: while RASP molecules bind to cellular biomolecules, disrupting their function and activating pro-inflammatory mediators, reproxalap inhibits this inflammation by binding the free aldehydes and reducing RASP levels as a result.

In the second quarter of 2021, results were published for the Phase Ib trial studying the effectiveness of reproxalap in reducing dry-eye signs and symptoms. The company says the agent demonstrated rapid, broad and clinically relevant symptomatic control in a cohort of 300 DED patients over 12 weeks of therapy. It also showed significantly greater improvement in signs of the disease vs. the vehicle, as demonstrated by fluorescein staining. Patients in the study reported the drops to be highly tolerable.

“We’re learning so many different pathways for upregulation and control of the inflammatory response,” says John Sheppard, MD, who practices at and is president of Virginia Eye Consultants and is a professor of ophthalmology at Eastern Virginia Medical School in Norfolk. “Aldehydes are very important in inflammation; The aldehyde species has a wide variety of tissue-destructive and cytokine-activating functions that are misdirected in autoimmune disease or inflammatory processes of aging. It turns out dry-eye patients have high levels of a byproduct of aldehyde metabolism: malonaldehyde. If you put a RASP-inhibitor drop, such as reproxalap, in the eye of a dry-eye patient, the decrease in that metabolite, malonaldehyde, corresponds to improvement in dry-eye signs and symptoms.”

Results were published last month from another Phase II clinical trial that compared ocular discomfort and itching symptom scores of reproxalap versus Xiidra in 56 patients with DED. They found that both patient-reported ocular discomfort ($p=0.002$) and itching ($p=0.01$) were statistically lower with reproxalap than with Xiidra.

Aldeyra is currently finishing Phase III trials to further evaluate the drug.

RGN-259 (RegeneRx)
RegeneRx has conducted a series of Phase III clinical trials since 2015 for its Tß4-based sterile and preservative-free eye drop, RGN-259, which has been approved for the treatment of neurotrophic keratitis in the United States since 2013. The drop’s active ingredient, Tß4, promotes corneal and ocular surface healing by facilitating epithelial migration and increasing cell-cell and cell-matrix contacts, which in turn reduces apoptosis and inflam-
You’re Invited

OTC for Dry Eye: An Implementation Workshop

What to expect:

• Discover over the counter (OTC) solutions for dry eye, how they work, why they work, how practices are implementing them.

• Explore a new way to implement OTC for dry eye relief with the Physician Guided Solutions Model.

• Choose the method of delivery to your patients from in-practice methods to remote methods with auto-delivery options for your patients’ convenience.

• Learn about MY OASIS™ platform for a Dry Eye Resource Center: Solution Fulfillment, Education, Compliance

Who Would Benefit from Attending:

• Optometrist
• Ophthalmologist
• Key Practice Coordinators/Planner
• Office Manager
• Front office team member
• Dry eye team

Commitment: 1.5 hour workshop

Call To Order: (844) 820-8940
Also Available on MY OASIS™ Platform.

www.oasismedical.com
customerservice@oasismedical.com

Scan to Schedule a Workshop

Oasis TEARS® & OASIS names & logos are registered trademarks of OASIS® Medical, Inc. 514 S. Vermont Ave, Glendora, CA 91741. LIT-OTCW-AD1 Rev 0 1.2022
mation in the cornea.

The company announced in March 2021 that the most recent clinical trial completed, ARISE-3, which enrolled 700 participants, didn’t meet its primary outcome measures. Still, the results demonstrated improvement in ocular grittiness at one and two weeks after treatment that was statistically significant, according to the company. RegeneRx notes that in all three clinical trials conducted so far (ARISE-1, -2 and -3), results have shown an improvement in various signs and symptoms of dry-eye syndrome, and the drug has proven safe.

The company says it will continue to analyze the clinical data and investigate the efficacy of RGN-259 and that it’s looking towards a pre-Biologics License Application (BLA) meeting with the FDA in the near future.

**Visomitin (Mitotech)**

Visomitin is a solution of SkQ1, a novel mitochondrial-targeted antioxidant currently being investigated in the treatment of various inflammatory ocular surface conditions including moderate to severe dry eye.

“The mechanism of action includes the inhibition of inflammatory breakdown products and mitochondrial metabolism,” says Dr. Sheppard. “This produces different types of effects including anti-inflammatory, anti-tear secretory deficiency and a regenerative effect on the lacrimal accessory gland tissue rejuvenation process, which may, although this is not yet documented, apply to other sources of tears such as meibomian glands, accessory lacrimal glands and goblet cells. It also has a direct effect on epithelial repair and healing.”

Results from VISTA-1, a Phase IIb/III clinical study that enrolled 450 patients, found that relative to the vehicle, SkQ1 demonstrated a statistically significant reduction of ocular discomfort by week four while maintaining an excellent safety profile and tolerability similar to that of an artificial tear. The more recent VISTA-2 Phase III trial, including 610 patients, had similar outcomes; both VISTA-1 and VISTA-2 demonstrated statistically significant improvement in conjunctival fluorescein staining vs. vehicle and improvement of best-corrected visual acuity at week four.

“Patients who have failed other medications indicated for dry eye may be great candidates for this new therapy because of the very new and novel mechanism of targeting mitochondrial metabolism,” Dr. Sheppard says. He notes that one unique aspect of this drug is that it “does more than fight inflammation because it targets mitochondria that present in all cell types on the ocular surface, from the cornea, conjunctiva and secretory apparatus to the lid and cutaneous tissues adjacent to the lid.”

The last trials designed to confirm these outcomes, VISTA-3 and VISTA-4, are scheduled to begin in the second half of 2022.

**CyclASol (Novaliq)**

CyclASol is an anti-inflammatory solution containing 0.1% cyclosporine A in a unique formula developed to treat DED. The company says the therapeutic approach involves the company-designed water-free technology, EyeSol, which is meant to increase the time the drug resides on the ocular surface and enhance bioavailability to target tissues, allowing the cyclosporine A to work more quickly and with maximum efficacy.

“The semifluorinated alkane molecules in EyeSol are water-free, don’t require preservatives and are able to solubilize a wide variety of active pharmaceutical ingredients, some of which aren’t very soluble in other vehicles,” says Dr. Sheppard. “Also, the semifluorinated alkanes have unique molecular characteristics; they create a drop that’s only 20 µl in size, much smaller than a standard solution or suspension, which is about 50 µl. Considering the tear film only holds about 20 µl to 30 µl in the cul-de-sac and on the surface of the eye, this medication won’t spill over on the cheek like virtually all other topical medications.”

The drop is in late-stage development after achieving positive results in three completed clinical trials. In its Phase Ib/III ESSENCE-1 trial including 328 patients with DED who were treated for 12 weeks, researchers found CyclASol to be superior to vehicle in total corneal fluorescein staining at week four. After two weeks, this difference was already statistically significant and remained so throughout the study. The treatment was also shown to be safe and well-tolerated.

Results of the latest trial in Phase III, ESSENCE-2, were just released by the company in December 2021. Designed to replicate and confirm the findings from ESSENCE-1, the study enrolled a larger cohort of 834 DED patients and found once again that improvement of total corneal fluorescein staining was achieved at week four. By this time point, nearly three in four patients (71.6 percent) improved by at least three grades in total corneal staining. Compared to vehicle-treated patients, those receiving CyclASol demonstrated statistically significant improvements across a range of common symptoms.

The company plans to conclude the drug’s clinical development program with a multicenter, 12-month safety extension trial (ESSENCE-2 OLE), which completed enrollment in the summer of 2021 and includes 202 patients.

**NOV03 (Bausch + Lomb)**

Another treatment in the pipeline that uses EyeSol technology is NOV03
(perfluorohexylkane). This drop was specifically developed for patients with meibomian gland dysfunction contributing to their dry eye, which studies have indicated is the case for a majority of DED patients.

“If approved, NOV03 may be the first pharmaceutical therapy in the United States indicated for this patient population,” says Joseph Tauber, MD, founder of Tauber Eye Center in Kansas City, Missouri.

The first Phase III trial, GOBI, enrolled 597 participants, half of which administered the drop twice a day and half of which administered it four times a day. The company reported that patients on either dosing regimen demonstrated an improvement in total corneal fluorescein staining and eye dryness (subjectively scored by the patient) vs. the control at eight weeks.

Midway through 2021, the company completed the latest Phase III trial, MOJAVE, which included 620 participants who received either NOV03 or a saline solution (the placebo). Both studies were able to meet their primary endpoints for reduction of the signs and symptoms of DED compared to the control saline groups.

Dr. Tauber notes that trials from the second phase had similar results: “In the Phase II clinical trial, SEECASE, the effect of improved total corneal fluorescein staining started as early as two weeks after start of treatment and was maintained over the entire duration of the trial for both treatment regimens (two and four times daily).”

Bausch + Lomb expects to conclude its investigation of NOV03 with the current ongoing 12-month safety extension trial, KALAHARI. The company anticipates filing a New Drug Application in the first half of this year.

**Lacripep (Tear Solutions)**

This therapeutic drop was developed to treat symptoms of dry eye and primary Sjögren’s Syndrome through the use of a proprietary synthetic fragment of lacritin, a natural tear protein that’s limited in tears of people with dry eye. The company says the solution is water-soluble and designed to work by restoring basal tearing and homeostasis of the ocular surface without causing irritation.

The Phase II, double-masked study involved 204 participants with dry eye caused by primary Sjögren’s receiving either 0.01% Lacripep, 0.005% Lacripep or a placebo solution, the second of which appeared to perform best among the cohort. Trial results were presented at ARVO 2021, one of the outcomes being that patients with moderate-to-severe dry-eye symptoms using the 0.005% concentration showed significant improvement in inferior corneal fluorescein staining and reduced levels of burning and stinging after two weeks, although the latter wasn’t significant at four weeks.

The company says it will continue conducting clinical studies to investigate the safety and efficacy of the drop, including its optimal dose and duration of administration.

Another protein therapy in the dry-eye pipeline is ECF843 (Novartis), which is in Phase II clinical trials.
In a study of 718 participants, the recombinant human lubricin (rh-Lubricin) protein has shown its ability to provide immediate symptom improvement likely by increasing lubrication across the ocular surface. The company says the drug is hypothesized to restore the function of the tear film, reduce friction and alleviate dry-eye signs and symptoms.

**HBM9036 (Harbour BioMed)**

This drug, with the proposed brand name Tanfanercept, is a tumor necrosis factor receptor 1 fragment. The mechanism of action involves the binding and blocking of TNF-α, which results in suppressed inflammation after drop use. The company released results from Phase II trials in 2020, which cited that Tanfanercept (0.25%) demonstrated significant improvements in signs with a good safety profile and rapid onset. The Phase III clinical trial began in March 2021, and the company expects to submit a BLA application to the FDA in 2022.

**AR-15512 (Aerie Pharmaceuticals)**

Investigational eye drop AR-15512 was formulated to tackle the signs and symptoms of DED through its active ingredient: a proprietary agonist of transient receptor potential melastatin 8 (TRPM8) cold thermoreceptor, which creates a comfortable cooling sensation across the eye, according to the company. Aerie explains that TRPM8 channels are cold-sensitive, found on the eyelid and cornea and play a role in helping the tear film maintain homeostasis. Increased TRPM8 activity can lead to increased tear production and blink rate, while its dysfunction may cause or worsen dry eye.

In the fall of 2021, Aerie released the Phase Ib (COMET-1) clinical trial results for AR-15512, which enrolled 369 dry-eye patients. Over an 84-day period, the drop showed and maintained significant improvement in both symptoms and signs, which was observed as early as week two. The company notes that efficacy was observed after the first dose and that the drop appeared to be safe and well-tolerated in both concentration levels tested (0.0014% and 0.003%).

Aerie reports that it plans to meet with the FDA in the first quarter of this year to discuss the results of Phase II and to begin planning the two anticipated Phase III efficacy studies, each lasting three months, as well as a final safety study.

**AZR-MD-001 (Azura Ophthalmics)**

This keratolytic drop treats MGD and evaporative DED. The Phase IIb study evaluated the drug’s safety and efficacy in treating 95 patients with MGD and found there was a statistically significant and clinically meaningful reduction of symptoms by the end of the three-month trial period in patients receiving the 0.5% or 1% concentration. More than half of the patients (58 percent) were asymptomatic after the three months, compared to 16 percent of patients in the control group. They also observed that in both concentration groups compared with controls, the number of glands secreting meibum showed significant improvements in as little as one month.

**TP-03 (Tarsus)**

TP-03 is currently undergoing trials as a novel treatment for Demodex blepharitis, a common type of blepharitis caused by an infestation of Demodex mites within the eyelash follicles. TP-03 is formulated with lotilaner, an anti-parasitic agent that works by paralyzing and eradicating Demodex mites through selectively inhibiting parasite-specific GABA-Cl channels.

“It’s a potent, non-competitive antagonist of insect and arachnid GABA-Cl channels and a highly lipophilic molecule, which may promote its uptake in the oily sebum of the hair follicle where the mites reside,” says Elizabeth Yeu, MD, a partner and practicing ophthalmologist at Virginia Eye Consultants and medical director of the Virginia Surgery Center. “Essentially, the treatment is able to target and kill the mites while being safe for use on humans.”

The company released results last June from the Phase Ib/III Saturn-1 pivotal trial including 421 Demodex patients who had more than 10 collarettes on the upper lid, at least mild erythema of the upper eyelid margin and at least 1.5 mites per lash on the upper and lower eyelids combined. Tarsus reports that TP-03 met both the primary and secondary endpoints and was well-tolerated. They note that 81 percent of patients on TP-03 achieved a clinically meaningful collarette cure (10 or fewer collarettes, grade 0 or 1) compared with 23 percent of patients who received the vehicle. They also report that 68 percent of patients on TP-03 achieved mite eradication (defined as a mite density of zero mites per lash) by day 43 compared with 18 percent for the vehicle.

“One in five patients experienced a complete erythema cure and 45 percent showed at least a one-grade improvement,” says Dr. Yeu. “Both results were statistically significant.
compared to vehicle, and very meaningful to me as a clinician and for my patients.”

TP-03 is currently being evaluated in the Phase III pivotal trial (Saturn-2) with the same primary endpoints. Results are anticipated to be released during the first quarter of this year. If the data is positive and similar to that from Saturn-1, the company plans to submit a New Drug Application this year.

**ST-100 (Stuart Therapeutics)**

At the beginning of this year, Stuart Therapeutics announced the Phase II trial results for its investigational drop for dry eye, ST-100. The 160-patient study found that the drug met the Schirmer’s Responder Rate endpoint at four weeks (defined based on FDA guidance as a statistically significant difference in the percentage of patients achieving a 10 mm or greater increase in Schirmer’s tear test scores). As early as day seven, ST-100 showed significant results in several symptoms and ocular surface staining scores, the company says.

Clinical trials will soon evolve to Phase III, the company says.

**SURF-100 and SURF-200 (Surface Ophthalmics)**

Surface Ophthalmics is developing two therapeutic drops for sufferers of dry eye, both of which use the company’s patented Klarity diluent as the vehicle: SURF-100 (mycophenolate sodium and betamethasone sodium phosphate), made for the treatment of chronic DED; and SURF-200 (betamethasone), which treats acute/episodic dry eye.

The two products are currently in Phase II clinical studies. The trial for SURF-100 is enrolling about 300 patients, and the trial for SURF-200 is enrolling between 120 and 140 patients. In the first two months of 2021, the company reported that the first patients in both trials had been dosed.

**GLK-301 (Glaukos)**

Rather than an eye drop, this topical cream, code-named GLK-301, is applied to the outer eyelid. The active ingredient, pilocarpine, is intended to help relieve DED signs and symptoms. The company announced last month that it had begun enrollment for the Phase II clinical trial, which will include 200 patients with DED, including 20 with Sjögren’s. The trial is meant to evaluate the safety and efficacy of GLK-301 applied twice daily to lids over four weeks, followed by a two-week safety follow-up period.

Three dose levels of GLK-301 will be tested and compared with placebo.

3. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification
IS REFERRAL PRACTICE IN YOUR FUTURE?

For young MDs considering their next steps, experts offer their perspectives on tertiary and quaternary care.

Christine Leonard
Senior Associate Editor

Working in a referral-only practice and dealing with diverse surgical complications can be highly satisfying, but the road to mastering the surgical techniques that you’ll encounter in tertiary or quaternary care is a long and difficult one.

In this article, veteran surgeons discuss the types of procedures they perform in tertiary- and quaternary-level practice, weigh some of the benefits and drawbacks and offer advice for young doctors who may be considering this path.

Referral Practice Basics
A tertiary or quaternary practice is most likely to be found in a university setting. “There’s more access to technology and clinical research and development at an academic center,” notes glaucoma specialist Brian Francis, MD, of the Doheny Eye Institute. “You also have greater access to teaching opportunities. There are tertiary-level private practices as well, though. They’re often group practices, and more common in retina than in glaucoma. I get referrals from other glaucoma specialists as well as some non-glaucoma specialists.”

Realistically, it’s easier to get into tertiary or quaternary practice if you have a mentor who practices at that level. However, your mentor won’t teach you everything. “A mentor will get you started, but things change in the field, and 10 years later, you should be adding on to what your mentor has taught you,” Dr. Francis says. “You need to have the desire to constantly be trying new things and developing techniques yourself.”

“There’s a good deal of patience involved as well,” he continues. “The surgeries are complex and require extra time with the patient, both in the chair and in the OR. This is a good place for those who want to be problem-fixers and pick up the pieces. If you’re not that type of person, or you want to deal with more straightforward cases, this might not be for you.”

He adds that the biggest advantage of quaternary practice is also its biggest disadvantage. “Quaternary practice is very exciting,” he says. “You deal with complex, intellectually stimulating problems. It never gets boring because you won’t be doing the same procedures day in and day out. The flipside is that it can be very stressful. In a quaternary practice, the buck stops with you. If you can’t fix it, there’s nobody else to send the patient to.”

Complex Procedures
When the surgery is more complicated than anticipated, or when the complexity level outpaces the surgeon’s comfort level, as Brandon Ayres, MD, of Wills Eye Hospital in Philadelphia puts it, those cases are usually referred to tertiary or quaternary subspecialists.

Cornea. Dr. Ayres says that one of the things he enjoys about being a cornea specialist in a largely quaternary practice is that he’s able to fix almost anything in the front of the eye. “Being able to fix the lens, iris and cornea allows me to be a bit more of a complete anterior segment surgeon,” he explains. “Many patients who come in with other anterior segment problems also end up with corneal problems. The
cornea tends to suffer from repeated abuse—multiple surgeries take their toll, and corneal edema is common.”

He says his surgical day is quite varied at Wills, which keeps his job interesting and him on his toes. “I see many patients for lens exchanges and dislocated IOLs,” he says. “Lens exchange patients are usually unhappy with the visual result they got—maybe the implant didn’t fully correct their vision or they’re unhappy with the quality of vision after a multifocal and want a lens exchange. We often see dislocated IOLs due to pseudoexfoliation or another preexisting condition that the patient has. Sometimes the support in the eye isn’t adequate to hold a lens and the surgeon opted to just hold off, or they had a problem placing the lens. We go back in and finish the surgery.”

“We become more facile at the procedures and learn additional tricks of surgery that can help various patients,” he continues. “The more tricks you learn, the bigger your toolbox becomes for helping other patients. The more you perform atypical procedures and techniques, the better you become at them.”

When dealing with such complicated cases, outside-the-box thinking is often necessary for finding a surgical solution to patients’ problems. This means employing some alternative techniques. “Alternative techniques aren’t commonly used,” Dr. Ayres says. “I would never claim to be a better surgeon than anybody else. I think my surgical skills are probably about average, but I’ve gotten a lot of exposure to these complex cases, and that’s allowed me to apply what I’ve learned in different ways to help patients with their unique problems. Someone who doesn’t have the privilege of dealing with these specialized issues on a day-to-day basis might encounter a case like this only once a year or every other year, but we get to work on them three to four times a day.

“We become more facile at the procedures and learn additional tricks of surgery that can help various patients,” he continues. “The more tricks you learn, the bigger your toolbox becomes for helping other patients. The more you perform atypical procedures and techniques, the better you become at them.”

Some alternative techniques involve holding an instrument differently or in a different hand. Others might repurpose an instrument. “One example of this, passed down by anterior segment specialists, is using the retinal cautery unit for iris repair,” Dr. Ayres explains. “We attach the cautery unit to our phaco device and cauterize the iris to reshape it for patients with iris damage (Figure 2). That’s not what the cautery unit was made for, but it works beautifully and helps us get a better result in iris repair.”

“Much of what we do consists of off-label procedures or difficult procedures, but many of those are what we enjoy the most,” says corneal specialist Sam Garg, MD, of the University of California Irvine, noting two of his favorites: Yamane fixation for an IOL exchange and performing DSEK in a complicated eye. “At my academic center, we see a lot of cases of corneal infections, corneal transplants and complications from cataract surgery such as corneal edema, dislocated lenses or a need for lens refixation. But part of being at a referral center isn’t always getting to do the ‘easy’ cases. Sometimes it involves cases with difficult patients who didn’t understand what they were getting into and now it’s your job to help them understand that nothing was done wrong in their original surgery, but that their expectations may have been unrealistic.”

• Retina. The patients whom Mitul Mehta, MD, sees at his UC Irvine-based retina practice usually fall into two groups, he says: either their disease was managed elsewhere and a complication developed afterwards, or the outside practice didn’t have the equipment necessary to perform a specific procedure. He often sees patients for diabetic retinopathy, tractional retinal detachments, ocular trauma, ruptured globe repair, intraocular foreign body removal, choroidal hemorrhages, dislocated IOLs that have fallen into the vitreous and aphakic patients who need a secondary lens but lack a capsule or zonules.

“For cases such as PVR detachments, where patients may have had previous failed surgeries, we remove the lens using a pars
plana lensectomy,” he says. “Oftentimes, the cornea is damaged as well. In those cases, we work with our cornea colleagues who perform a corneal transplant with a temporary keratoprosthesis, which allows us to obtain a good enough view through the cornea to remove the lens and work in the vitreous cavity. We often put in a scleral buckle or do a large retinectomy, where we remove large sections of the retina to allow the retina to lie flat after peeling the membranes. In cases where the membranes are very stuck to the retina and the retina is detached, we’ll put in a chandelier light, so we have two hands available to peel the membrane off the retina.

“When we encounter intraocular foreign bodies, we do a vitrectomy to remove the item from the back of the eye,” he continues. “If it’s metallic, we use an intraocular magnet to pick it up, so as not to damage the retina while trying to grab the item. If it’s embedded in the retina, we make sure to secure and stabilize the retina before we pull it out in order to avoid the eye filling with blood. The entry wound isn’t usually suitable for removing the foreign body, so we close the entry wound first and make a separate wound to remove the item. The latter goes for dislocated intraocular lenses—we often need to make a new wound to remove the lens or the lens fragments, after we cut it. We’ll fixate the new lens to the wall of the eye.”

• Glaucoma. Most of the cases Dr. Francis sees have either failed prior glaucoma procedures or have complications from prior glaucoma surgeries, such as malpositioned MIGS devices or malpositioned tubes, leaking trabeculectomies, dysesthesia blebs, blebitis or tube erosions.

“In my practice, I also do a lot of UGH and IOL malposition cases,” he adds. “I got into treating UGH syndrome because one of my specialties is using the ocular endoscope system for doing ECP and lowering aqueous production, but also for intraoperative intraocular viewing. I can look at the sulcus and anterior retina in real-time and diagnose and treat some of these weird problems.”

He also uses the endoscope to check for IOL problems in the sulcus, foreign bodies, other causes of UGH syndrome and malpositioned tubes. “These are some of my favorite surgeries,” he says. “I also enjoy the MIGS procedures, and I do a fair number of tube revisions too, though they aren’t as enjoyable because they can be a little difficult sometimes.”

He says he often combines procedures to find alternative ways of controlling patients’ pressures. “If a patient has a recurring tube erosion, we’ll find an alternative position for it and place it in the pars plana or sulcus to keep it away from the cornea or the limbus in order to reduce corneal damage and the possibility of erosion. If we have to take them out, we can combine some of the non-filtering procedures such as ECP or Micropulse CPC with or without the angle-based MIGS procedures as well.”

Uncomplicating the Discussion

Many patients seen in tertiary and quaternary care are fixated on why their complication occurred or what the other doctor did “wrong.” “The patients who come to us are already not doing well,” Dr. Ayres notes. “Many are angry, scared or upset, and they’re looking to me to correct a complication or problem that was encountered during their surgery or was the result of a surgery. When I’m managing these patients, I’m not only thinking about how to achieve the best outcome, I’m also trying to...
Only Ocular Response Analyzer® G3 measures Corneal Hysteresis (CH) and Corneal Compensated IOP (IOPcc) using patented technology to assess the unique corneal biomechanical properties of your patient. Corneal Hysteresis has shown to be an independent risk factor and more predictive of glaucoma development and progression than CCT or IOP1-3. Using biomechanics, IOPcc is less influenced by corneal properties than Goldmann applanation tonometry4.

MEASURE BEYOND PRESSURE WITH CORNEAL HYSTERESIS.

WATCH THE VIDEOS AT REICHERT.COM/ora
make sure I shine a positive light on the referring surgeon.

“A patient may say, ‘How could this have happened? Why me? Did the surgeon do something wrong?’ I tell them that all surgeons experience complications, including myself,” he says. “Nobody’s perfect. Some things are out of the surgeon’s control, such as if a patient has some bleeding or a floppy iris. I often tell patients, ‘You’re lucky that that surgeon was there to take care of this and limit the potential problems to where they are so we can still get you fixed. Had this been a less skilled surgeon, you may have been in a worse place than you are now.’ We never tell patients that something was ‘messed up.’”

Dr. Mehta advises every specialist to have a standard spiel prepared for their patients before surgery. “I always make sure to mention to all my patients that people can have strange reactions to medications or the surgery itself that could lead to loss of the eye entirely,” he says. “I impress upon them that there’s always a risk to intraocular surgery, but that we do the surgeries because we believe they’ll benefit the patient. You can go into the specific details of the more common risks for a given surgery, but I always start with that so the patients understand that surgery is serious and shouldn’t be taken lightly, even for a procedure that I would consider simple for me.

“Patients don’t know what a procedure really entails or what the postoperative course is going to be like,” he continues. “They need to know what they’re getting into. Many patients believe all surgeries can be done with lasers outside the operating room. There’s a lot of education that needs to happen. It doesn’t have to take long, but it should hit the major points.”

Accepting Risk

Surgeons who work in tertiary and quaternary care say they find their jobs highly satisfying because of the challenging cases and cutting-edge procedures they often perform. However, they all agree that higher reward also means higher risk. “We’re dealing with patients who have bigger-than-average problems or are more complicated than average,” Dr. Ayres says. “Not every patient is going to have a good outcome. When you’re sent patients who already have a surgical complication, you’re accepting some of the risk that was given to you by the other doctor.”

Some patients will develop complications such as retinal detachments around the period when you first evaluated them and their scheduled surgery. Did the complication develop after you saw the patient or did you miss it on the evaluation? “You’re taking on some of the risk of not seeing that retinal detachment complication and not sending that patient to see a retinal specialist,” Dr. Ayres says.

He uses a measure of caution. “I’ll tell a patient, ‘I think I can fix your problem, but I want you to see a retinal specialist in a couple of days to make sure your retina makes it through the surgery.’ I cover my bases with help from my colleagues who are experts in other fields to make sure I’m not missing anything, and that we give the patient the best outcome and care possible.”

As with any case, but especially with complex patients, it’s important to document your cases thoroughly. “I don’t have special insurance for doing complicated cases, so I make sure to document everything well in the chart and discuss things well with patients,” Dr. Ayres notes. “That helps to limit your liability.”

Accepting Limitations

Dr. Garg points out that not every case will have a surgical solution. “You have to consider whether intervention is the right thing for the patient,” he says. “Sometimes surgery won’t achieve meaningful improvement, and it’s better to tell the patient that more surgery won’t be fruitful. That takes time to understand. When you first start practice, you may believe that you can help any patient who comes in, but these aren’t straightforward cases. We do our best, and sometimes we hit a home run but other times we don’t. That’s part of the job.

“It can be a difficult conversation to have,” he continues. “The patient may not understand why you’re not doing more surgery. They may have believed, after having seen other doctors, that you could help them, and unfortunately, that’s not always the case.”

Dr. Mehta says that the patients whom retinal specialists are unable to treat are usually those who have a disease for which there are no treatments, such as dry macular degeneration with geographic atrophy. “Currently, there’s nothing FDA-approved and nothing on the horizon that looks like it’ll improve patients’ vision,” he says. “Everything right now is focused on slowing the progression of the disease. These patients aren’t going to get any better no matter what I do, but I can make sure to follow the other eye, look for other diseases and try to minimize the effects of their disease.”

“There are some glaucoma cases where there’s nothing you can do, but it’s pretty rare,” says Dr. Francis. “Unless the patient has no...
light perception, there’s usually a glaucoma procedure you can offer. It pays to be familiar with all of them to increase your options.”

**Time Isn’t Money**

“If you have a business-development mindset and want to build a large practice and make a lot of money, quaternary practice isn’t the best way to do it,” Dr. Francis points out.

Performing these complex procedures can take a long time, and the pay isn’t always equivalent to the amount of time they take. “A PVR detachment that takes two to three hours to repair doesn’t pay any more than a retinal detachment repair with a mild membrane peel,” Dr. Mehta says. “A case like that could take a fraction of the time and pay almost as much or just as much as a case that takes several hours.”

“Corneal transplant surgeries or IOL exchanges lose you time in the OR, in a sense,” Dr. Garg notes. “These surgeries take much longer than a 10- to 15-minute cataract surgery and decrease your opportunity for seeing ‘revenue-generating’ patients because you see complex patients many more times than you would a cataract patient in the global period.

“At the same time, the satisfaction level is different,” he continues. “When you have this skillset, it’s not all about dollars and cents. It’s about where you can make the biggest impact for these patients and for your community. If you’ve been trained to do these special techniques, you can’t look at your practice in only financial terms, because if you do, it doesn’t always make sense to take on these more challenging cases.”

**The Business of Referrals**

One thing that many young doctors don’t consider as residents or fellows is where their future patients will come from. “It’s way more work than I thought it was going to be,” Dr. Ayres admits. “I don’t advertise myself to the general public. I rely on other doctors to send me their problematic cases. I not only need to perform for the patients so that they do well, I also need to perform well so that referring doctors who may feel responsible for some of the patient’s complication or complexity will think of me to fix the problem. I need to put myself out in the community and show people my work, like a portfolio. I never thought that would be part of my business, but it’s a major part.”

Dr. Mehta says it’s fundamentally important that you get to know your community if you’re embarking on tertiary or quaternary practice. “Every area has some sort of ophthalmology society, and it’s a good idea to become a member of those societies,” he says. “Go to the meetings and get to know who the other doctors are in your area so they can refer patients to you. They need to know what you can do. One benefit of being a specialized surgeon is that there will always be a demand. Complications happen, regardless of region.

“I’m a member of my local ophthalmology society,” he continues. “I’m on the board, and the reason I’m on the board is that I went to every meeting and people saw me there and saw that I was active. I have separate business cards with my cell phone number on them that I give to other doctors. They call or text me all the time and send me patients. This helps me build my practice.”

He says it’s a good idea to offer continuing education for local optometrists. “We don’t do that at the university, but we do offer CME for general ophthalmologists,” he notes. “Once word gets out that you can handle very complex cases, people will send patients your way. You’ll be sent some routine cases too. The routine cases will fill up your regular clinic days and help to build your practice at the beginning. Sometimes I get a patient who doesn’t have a retinal issue, and I’ll either send them to the proper person or if it’s simple, I’ll fix it myself.”

**Advice For Young MDs**

Mastering complex surgical techniques is a long but rewarding process. Here are some words of wisdom to keep in mind for expanding your skillset and setting yourself up for success:

- Stay current with your CME. “Continuing education is very important,” Dr. Francis says. “The major societies all have programs for skills transfer that are very valuable. You can learn from experts and develop new skills at meetings, such as suturing IOLs or IOL fixation or different types of glaucoma procedures. We run a MIGS lab at the Academy every year. You may attend a lab course and end up deciding that it isn’t for you. That’s okay, but at least you tried it and made an effort to incorporate something new into your practice.”

Dr. Garg adds that “Even if you don’t do these complex techniques on a day-to-day basis, sometimes just knowing how to approach a difficult situation can prevent patient harm and morbidity. You never know when you’ll be in a situation when things may go awry. These techniques can be difficult to master, and they take more time and effort to learn.

“It doesn’t always go well in the beginning,” he adds. “You might see Dr. Ayres do a video and try it yourself, and it doesn’t go the way Dr. Ayres showed it. There’s an opportunity cost to learning these techniques, but the payout is huge from a personal satisfaction standpoint and from a patient-benefit standpoint.”

- Seek feedback from your mentors and colleagues. “Whether you feel comfortable with a procedure or not, you have to make use of all the resources you have available to you: your network, societies like ASCRS and AAO, mentors, published talks and videos, lectures and courses,” Dr. Garg says.

The network of mentorship
and professional societies is key for expanding your skillset, but ophthalmology meetings aren’t everyday occurrences. “Daily social interaction with your colleagues is just as important,” Dr. Mehta says. “If you practice in a group setting or at an academic institution, you have easy access to your colleagues to discuss cases or comanage with other specialists and subspecialists. That’s a major advantage.”

• **Challenge yourself to leave your comfort zone.** “Many of the techniques I perform now I didn’t learn during residency or fellowship,” Dr. Ayres says. “YouTube, ASCRS, AAO and wet labs are great resources for learning. Talk to friends who’ve done these cases before and get outside your comfort zone a bit. I encourage our residents and fellows to keep an open mind,” he says. “One of the things I like to tell our fellows is, ‘Say yes—if you feel comfortable.’ You won’t learn the skills unless you try. Before I became very comfortable doing these procedures, I’d tell patients, ‘I’m going to do the absolute best job I can, but if for some reason I’m not able to get the lens out, we’re going to leave it and you’ll be okay. My goal is to do no harm. I think I can help you.’ You try and try and get better and better. And eventually it’s really a rare day that you can’t get a lens exchange done.”

  • **Set personal boundaries.** “Nobody can last as a resident or a fellow forever,” Dr. Mehta says. “Working 80 or 100 hours a week isn’t sustainable if you want to have a life outside of work. You need to set boundaries and set up a system where there will be people to cover you for calls or your patient messages—patients call us with very simple questions, and they do expect an answer. Someone from your office should respond to them. In an ideal situation, the doctor does only what the doctor alone can do and not too much more than that. This isn’t the case for most practices or universities, but that’s a good goal to have. You should try to be supported as much as you can. Delegating tasks will help your days move and give you extra time to think.”

  These specialists agree that tertiary and quaternary care are highly satisfying fields. “You’re helping patients who wouldn’t be able to get that level of care elsewhere,” Dr. Francis says. “You need the surgical skillset; you need to make yourself available for the patient and that Friday afternoon high-pressure case; and you need to build rapport with both the patient and the referring doctor,” he says. “Communicate well with the patient and with the referring doctor about the patient’s status and what you’ll do for the patient.”

  “Many people in quaternary or tertiary referral tend to be academically-minded and do some research or go to conferences,” he continues. “In order to get the most out of conferences, you need time to think. You can’t be running 24/7. I set aside half days when I don’t see patients. During that time, I work on academic pursuits that interest me. That’s what keeps you excited, instead of getting burnt out.”

  • **Remember the “Three As” of building a practice.** These are ability, availability and affability, says Dr. Francis. “You need the surgical skillset you need to make yourself available for the patient and that Friday afternoon high-pressure case; and you need to build rapport with both the patient and the referring doctor,” he says. “Communicate well with the patient and with the referring doctor about the patient’s status and what you’ll do for the patient.”


Figure 3. Anterior segment surgeons sometimes turn to the cautery unit (which was intended for retinal applications) to reshape the iris. In this case, a young female patient presented with a ruptured globe due to blunt-force trauma, a traumatic cataract and an incarcerated iris. After cataract removal and enlargement of the capsulotomy, the iris was repaired using a sliding knot and thermal iridoplasty. The iris edges at the scleral incarceration were brought together with 10-0 polypropylene and a CIF-4 needle, forming a teardrop-shaped pupil. A modified sliding knot (also known as a modified Siepser knot) was tied with three throws to close the iris defect. Using 25-gauge intracocular diathermy on a very low setting on the anterior segment machine (about 11 to 12 on the Alcon Centurion), small cautery burns were made on the iris (A) to re-shape and round out the pupil (B). Dr. Ayres advises against being overly aggressive with cautery since there will be some transillumination defects where the cautery burns were made.
VIRTUAL FIELD

The Virtual Field provides greater efficiencies with reduced testing time and the ability to test multiple patients at once with no eye patch necessary. The mobile, lightweight design allows patients to be tested anywhere with wifi access, and it is easier to clean than traditional perimeters.

FEATURES
- Progression analysis
- Monocular or binocular testing
- Access results from any laptop, tablet, or mobile device
- Audio instructions and error prompts in 34 languages
- Download reports as PDF/JPG files for upload into any EHR
- Qualifies for ADA tax credit

LEARN MORE

800-LOMBART
LOBARTINSTRUMENT.COM

Lombart is part of Advancing Eyecare one alliance • Seven industry leaders • Comprehensive Ophthalmic Solutions
A Review of Retinitis Pigmentosa

A rundown of retinitis pigmentosa’s etiology, diagnostic findings and current and future treatment options.

Inherited retinal diseases, including retinitis pigmentosa, have been the subject of therapeutic clinical trials, including the safe delivery of gene therapy to the subretinal space, with encouraging results. Affecting approximately 1/4,000 individuals worldwide, RP represents one of the leading causes of vision loss, with a broad spectrum of genetic and phenotypic heterogeneity. According to RetNet (https://sph.uth.edu/retnet/), a publicly available database of genes and loci mapped to inherited retinal diseases, at least 150 genes have been associated with syndromic and non-syndromic retinitis pigmentosa.

Here, we’ll discuss the clinical findings, diagnostic modalities and current clinical trials associated with RP.

Mechanism and Findings

RP is characterized by progressive vision loss due to abnormalities of the retinal photoreceptor cells or the retinal pigment epithelial cells. Usually the disease begins with damage and loss of rod cells, leading to nyctalopia and defective dark adaptation, which are the common initial concerns for patients. Peripheral vision loss secondary to rod dysfunction occurs early in the disease course, although it may not be recognized by an affected individual. Secondary changes in the retinal cellular milieu due to loss of rod cells eventually result in loss of cone cells. Thus, the visual field is progressively reduced in concentric rings, leading to tunnel vision and ultimately, central field loss in end-stage disease.

Other findings of RP include posterior subcapsular cataracts (50 percent of cases) and photopsias. Less-common clinical findings in patients with RP include cystoid macular edema, macular holes and epiretinal membrane formation.

Due to the large number of causative genes and known phenotypic variance associated with RP, the disease’s clinical findings, onset and progression may differ considerably between affected individuals.

RP can be inherited in the three major mendelian patterns, but can also present in isolated or simplex cases. Classically, X-linked RP patients have an earlier onset and worse prognosis, followed by autosomal recessive patients, with intermediate outcomes; and finally, dominant forms have more variable presentations and better prognoses.

The differential diagnosis for RP can be further refined by age of onset. Although most individuals are diagnosed in early adulthood, a distinct subset of cases falls within the early-onset spectrum of diagnoses, which include Leber congenital amaurosis and early-onset severe retinal dystrophy (EOSRD)/severe early-childhood-onset retinal dystrophy (SECORD). LCA represents the most severe phenotype, characterized by profound vision impairment at birth or during the first months of life. Because pigmentary changes may only present later in life, symptoms such as nystagmus, poor object tracking and poor pupillary responses aid in the diagnosis. Electroretinogram signals are either extinguished or severely reduced. In contrast, EOSRD /SECORD are distinguished by residual, and sometimes improving, visual acuity and function; slightly preserved ERG signals; and later onset of symptoms, generally around or before the age of 5 years.

RP can be classified as non-syndromic (affecting only the retina) or syndromic (affecting other tissues and organs). Systemic findings often associated with syndromic RP diagnoses are summarized in Table 1. The most common form of syndromic RP is autosomal recessive Usher syndrome, the leading cause of genetic deafness-blindness. There are three types of Usher syndrome (I, II, III) with several subtypes, reflecting a combination of clinical and genetic findings. The second most common form of syndromic RP is Bardet Biedl.
syndrome, an autosomal recessive disorder characterized by obesity, postaxial polydactyly, cognitive impairment, hypogonadotropic hypogonadism, genitourinary defects and renal disease.

**Imaging and Testing**

When working up a patient, the following imaging methods and tests can help clinch the diagnosis of RP:

- **Fundoscopic examination.** The classic triad in RP consists of peripheral bone spicule pigment deposition, blood vessel attenuation (sometimes sclerotic vessels) and optic disc pallor. Bone spicule pigmentation usually develops in the mid-stages of the disease, starting at the mid-periphery, and moves toward the macula as the disease progresses. Pigmentation consists of retinal pigment epithelium cells that have detached and migrated to the inner retina after photoreceptor death. The attenuated vessels seen in patients with RP are believed to be due to either reduced metabolic demand or vasoconstriction and reduced blood flow resulting from a hyperoxic state after the loss of oxygen-consuming photoreceptors. Loss of the retinal nerve fiber layer occurs in the late stages of the disease; therefore, optic nerve pallor isn’t necessarily synonymous with ON atrophy. Potential causes for nerve pallor include ischemia of surrounding blood vessels due to location within a watershed area, which leads to diminishment of traditional color of the ON, or astrocytic and cotton-wool-spot-like gliosis caused by the retinal degenerative process.

- **Full-field electroretinography.** ERG is considered the gold-standard modality for diagnosing RP, establishing baseline function and monitoring RP progression. ERG can detect photoreceptor dysfunction even when changes on clinical exam or imaging modalities are minimal. Full-field ERG findings in RP patients include decreased rod amplitude, maximum, oscillatory, cone and flicker responses. Initially, individuals with RP have a decreased scotopic response (reflecting rod dysfunction), followed by prolonged B-wave implicit times. The eventual involvement and loss of cone photoreceptors leads to reduced amplitude of the photopic, maximum and 30 Hz flicker responses. ERG responses may be wholly extinguished in advanced stages of the disease.

Visual field testing is also suitable for establishing baseline function and monitoring disease progression. In the early stages of RP, visual field measurements show variable peripheral vision loss, progressing to a ring scotoma consistent with the tunnel vision described in the late stages of the disease. In a Goldmann visual field testing study, it was found that annual rates of decline in VF area for V4e, III4e, and I4e targets were 7.5, 10.7 and 12.5

---

**Table 1. Features associated with forms of syndromic RP**

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensorineural hearing loss</td>
</tr>
<tr>
<td>polydactyly</td>
</tr>
<tr>
<td>trunkal obesity</td>
</tr>
<tr>
<td>endocrine abnormalities (e.g., diabetes)</td>
</tr>
<tr>
<td>learning disabilities</td>
</tr>
<tr>
<td>renal defects and malformations</td>
</tr>
<tr>
<td>hypogonadism (males)</td>
</tr>
<tr>
<td>genital abnormalities (females)</td>
</tr>
<tr>
<td>nystagmus</td>
</tr>
<tr>
<td>ataxia</td>
</tr>
<tr>
<td>peripheral neuropathy</td>
</tr>
<tr>
<td>fat malabsorption</td>
</tr>
<tr>
<td>optic atrophy</td>
</tr>
<tr>
<td>dilated cardiomyopathy</td>
</tr>
<tr>
<td>liver fibrosis</td>
</tr>
<tr>
<td>congenital cataracts</td>
</tr>
<tr>
<td>keratoconus</td>
</tr>
</tbody>
</table>

---

**Figure 1. A case of advanced RPGR-X-linked RP.**

A) Pseudo-color fundus photography of the right eye shows classical findings of bone spicule pigmentation, attenuated blood vessels and optic nerve pallor. B) A fundus auto-fluorescence photograph of the same eye, showing an ellipsoid-shaped hyperautofluorescent ring.
percent, respectively. Mean annual VF loss was 10.3 percent for autosomal recessive, 2.7 percent for autosomal dominant and 7.2 percent for X-linked patterns of inheritance. OCT is used to assess retinal morphological changes in patients with RP. OCT performed early in the disease course can show disorganization of the outer retinal layers. With disease progression, decreased thickness of the outer nuclear layer can be observed. Late stages of RP are characterized by the complete loss of both the outer segment and the outer nuclear layer, with the inner retinal layers remaining relatively well preserved. Previous studies have described a correlation between structure captured by OCT and retinal function and show that retinal thinning (particularly foveal thinning) correlates with decreasing visual acuity and visual fields. OCT is also used to monitor the presence and progression of CME, macular cysts and macular holes in patients with RP. Of note, CME associated with RP can be treated with topical carbonic anhydrase inhibitors with variable results. In some cases, patients that do not respond well to topical therapy may require an oral CAI.

**Fundus autofluorescence.** FAF is commonly used to assess disease stage and progression. In FAF, areas of hypofluorescence representing atrophy of photoreceptors have been found to correlate with visual field defects observed by Goldmann perimetry, making them adequate complementary tests. Several FAF patterns are considered typical in RP, such as a hyper-autofluorescent ring or an abnormal central hyper-autofluorescence. This hyperfluorescent ring, also named the Robson-Holder ring, delineates the border between normal and disrupted inner and outer segment junctions, supported by OCT imaging. Significant loss of photoreceptors will be found outside the ring compared to inside it. The size of the ring negatively correlates with the remaining visual function, measured by perimetry.

**Genetic Testing**

In 2022, genetic testing is a cornerstone in the diagnosis and management of retinitis pigmentosa. In most cases, comprehensive next-generation sequencing can be performed at minimal to no cost to the patient, with multiple sponsored, open-access gene panels commercially available. Results are only available to patients and providers within weeks, providing diagnostic information that often impacts prognosis and management. However, causative genetic variants are identified in about 60 percent of cases, leaving a significant portion of cases with an undetermined genetic etiology. Furthermore, the ubiquitous presence of variants of uncertain significance can complicate the interpretation of results. Nevertheless, with increasing genetic testing rates and the continuous addition of genes to panels, our knowledge of the genetic etiologies of IRDs will likely continue to increase the diagnostic rates.

When considering genetic testing, ophthalmologists should be aware of some potential pitfalls such as false-positive rates, and differences in content and coverage of next-generation sequencing panels and other currently available genetic tests.

---

Full-field ERG of a patient with severe late-stage X-linked RP showing extinguished (isoelectric) (a) rod/scotopic (dim light response in dark adaptation), (b) maximum (combined rod and cone response to maximum intensity light in dark adaptation), (c) cone/photopic (bright light response in light adaptation) and (d) 30 Hz flicker responses OU.
This is where you’ll find C3, the linchpin of complement overactivation in the growth of GA lesions. C3 is where all three complement pathways converge, driving multiple damaging downstream effects— inflammation, opsonization, and formation of the membrane attack complex. All of this can lead to permanent retinal cell death in the pre-lesion, which is where your patients have the most to save.2,3
<table>
<thead>
<tr>
<th>Clinical Trial #</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Phase</th>
<th>Status</th>
<th>Vector</th>
<th>Administration Route</th>
<th>Country</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03328130</td>
<td>arRP</td>
<td>PDE6B</td>
<td>I/II</td>
<td>Recruiting</td>
<td>AAV2/5</td>
<td>Subretinal</td>
<td>France</td>
<td>Horama SA</td>
</tr>
<tr>
<td>NCT03252847</td>
<td>XLRP</td>
<td>RPGR</td>
<td>I/II and II/III</td>
<td>Active, not recruiting</td>
<td>AAV2/5</td>
<td>Subretinal</td>
<td>US/UK</td>
<td>MeiraGTx Holdings/Janssen</td>
</tr>
<tr>
<td>NCT03316560</td>
<td>XLRP</td>
<td>RPGR</td>
<td>I/II</td>
<td>Recruiting</td>
<td>AAV2</td>
<td>Subretinal</td>
<td>US</td>
<td>AGTC</td>
</tr>
<tr>
<td>NCT04850118</td>
<td>XLRP</td>
<td>RPGR</td>
<td>II/III</td>
<td>Not yet recruiting</td>
<td>AAV2</td>
<td>Subretinal</td>
<td>US</td>
<td>AGTC</td>
</tr>
<tr>
<td>NCT03116113</td>
<td>XLRP</td>
<td>RPGR</td>
<td>I/II</td>
<td>Completed</td>
<td>AAV8</td>
<td>Subretinal</td>
<td>US/UK</td>
<td>Nightstar</td>
</tr>
<tr>
<td>NCT04123626</td>
<td>adRP</td>
<td>RHO (Pro23His)</td>
<td>I/II</td>
<td>Recruiting</td>
<td>QR-1123</td>
<td>Intravitreal</td>
<td>US</td>
<td>ProQR Therapeutics NV</td>
</tr>
<tr>
<td>NCT00999609</td>
<td></td>
<td>RPE65</td>
<td>Completed</td>
<td>FDA-Approved</td>
<td>AAV2</td>
<td>Subretinal</td>
<td>US</td>
<td>Spark</td>
</tr>
<tr>
<td>NCT03374657</td>
<td>arRP</td>
<td>RLBP1</td>
<td>I/II</td>
<td>Recruiting</td>
<td>AAV8</td>
<td>Subretinal</td>
<td>Sweden</td>
<td>NOVARTIS</td>
</tr>
<tr>
<td>NCT01482195</td>
<td>arRP</td>
<td>MERTK</td>
<td>I</td>
<td>Completed</td>
<td>AAV2</td>
<td>Subretinal</td>
<td>Saudi Arabia</td>
<td>King Khaled Eye Hospital</td>
</tr>
<tr>
<td>NCT01505062</td>
<td>arRP</td>
<td>MYO7A</td>
<td>I/II</td>
<td>Terminated</td>
<td>N/A</td>
<td>Subretinal</td>
<td>US</td>
<td>Sanofi</td>
</tr>
<tr>
<td>NCT03780257</td>
<td>arRP</td>
<td>USH2A</td>
<td>I/II</td>
<td>Active, Not yet recruiting</td>
<td>QR-421a</td>
<td>Intravitreal</td>
<td>US</td>
<td>ProQR</td>
</tr>
<tr>
<td>NCT02320812</td>
<td>RP</td>
<td></td>
<td>II</td>
<td>Completed</td>
<td>Human retinal progenitor cells</td>
<td>Intravitreal</td>
<td>US</td>
<td>jCyte</td>
</tr>
<tr>
<td>NCT04604899</td>
<td>RP</td>
<td></td>
<td>II</td>
<td>Active, not recruiting</td>
<td>Human retinal progenitor cells</td>
<td>Intravitreal</td>
<td>US</td>
<td>jCyte</td>
</tr>
<tr>
<td>NCT02464436</td>
<td>RP</td>
<td></td>
<td>I/II</td>
<td>Recruiting</td>
<td>Human retinal progenitor cells</td>
<td>Subretinal</td>
<td>US/UK</td>
<td>ReNeuron</td>
</tr>
<tr>
<td>NCT04284293</td>
<td>RP</td>
<td></td>
<td>I</td>
<td>Recruiting</td>
<td>CNS10-NPC</td>
<td>Subretinal</td>
<td>US</td>
<td>Cedars-Sinai Medical Center</td>
</tr>
<tr>
<td>NCT04925687</td>
<td>RP</td>
<td></td>
<td>I</td>
<td>Recruiting</td>
<td>Autologous CD34+</td>
<td>Intravitreal</td>
<td>US</td>
<td>University of California, Davis</td>
</tr>
</tbody>
</table>

**Optogenetics**

<table>
<thead>
<tr>
<th>Clinical Trial #</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Phase</th>
<th>Status</th>
<th>Vector</th>
<th>Administration Route</th>
<th>Country</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02556736</td>
<td>RP</td>
<td></td>
<td>I/II</td>
<td>Active, not recruiting</td>
<td>AAV2</td>
<td>Intravitreal</td>
<td>US</td>
<td>Allergan</td>
</tr>
<tr>
<td>NCT03326336</td>
<td>RP</td>
<td></td>
<td>I/II</td>
<td>Recruiting</td>
<td>AAV2</td>
<td>Intravitreal</td>
<td>US, UK, France</td>
<td>GenSight</td>
</tr>
<tr>
<td>NCT04278131</td>
<td>RP</td>
<td></td>
<td>I/II</td>
<td>Recruiting</td>
<td>AAV</td>
<td>Intravitreal</td>
<td>US</td>
<td>Bionic Sight</td>
</tr>
<tr>
<td>NCT04945772</td>
<td>RP</td>
<td></td>
<td>II</td>
<td>Recruiting</td>
<td>AAV2</td>
<td>Intravitreal</td>
<td>US</td>
<td>Nanotherapeutics</td>
</tr>
</tbody>
</table>
Thus, pre-test phenotyping, consisting of obtaining a detailed medical history and reviewing diagnostic testing and imaging, is fundamental prior to ordering genetic testing in order to interpret results accurately. Additionally, working with a genetic counselor who can assist in panel selection and communicating testing results to patients, as well as education on prognosis, inheritance and natural history, should be considered and is highly recommended when available.

**Vitamin Supplementation**
Several studies have evaluated the use of vitamin supplementation, particularly vitamin A, in RP patients. Although early trials reported clinical benefits, later studies have shown that the efficacy of vitamin A in slowing disease progression is inconclusive. Furthermore, some cases of suspected RP can present similarly to Stargardt disease, which is caused by mutations in the ABCA4 gene that result in vitamin A metabolism dysfunction, leading to the accumulation of the A2E by-product and lipofuscin deposits in the macula. Thus, until this condition has been ruled out, particularly by genetic testing, patients should refrain from using any vitamin A or vitamin A-containing food, to decrease the risk of worsening. Patients can be advised to use supplements such as lutein and zeaxanthin (found in AREDS2 formulations such as PreserVision and Ocuvite) commonly offered for accessibility for surgical procedures, privileged environment, as well as its (editing). The retina’s immune-privileged environment, as well as its accessibility for surgical procedures, make it a suitable candidate for this type of approach.

Clinical trials assessing therapies that target various specific genes implicated in RP are currently under way:

— **RHO-related disease due to P23H mutations, QR-1123 (AURORA trial, ProQR Therapeutics NV).**
QR-1123 is an antisense oligonucleotide (ASO) designed to exclusively target the mutant P23H mRNA in RHO, which has been reported to account for 10 percent of autosomal dominant cases in the United States. ASOs have been shown to reduce the expression of the mutant mRNA through specific nucleotide pairings using a mechanism called RNase H mediated cleavage, while preserving the expression of the wild type. In vivo mouse models showed a 40-percent reduction of P23H mRNA with preservation of WT RHO and improvement in scotopic responses in ONL thickness. The AURORA trial is currently recruiting patients 18 years of age or older to evaluate the safety and tolerability of intravitreal injections of QR-1123, through open-label single-dose cohorts and randomized repeat-dose cohorts.

— **USH2A-related disease, QR-421a (STELLAR trial, ProQR Therapeutics NV).** Similarly, QR-421a is an RNA-based therapy designed to treat Usher syndrome type II. This therapy uses an exon-skipping approach where ASOs bind specifically to the USH2A RNA and exclude exon 13 from the RNA, leading to retinal cells that produce a shorter but functional copy of the USH2A protein. Interim results from their STELLAR trial showed that the therapy was adequately tolerated across all doses with no significant adverse events observed. Mean visual acuity improved by six letters in treated patients, while patients with advanced disease improved by 9.3 letters. At week 12, the mean change from baseline in the number of loci with improved static perimetry was 9.2 loci in treated eyes versus 6.1 in untreated eyes. OCT imaging also demonstrated stabilization of retinal architecture in the treated eyes versus sham and untreated eyes. (Results available at [https://www.proqr.com/files/2021-09/Euretina%20%282021%29%20DG%20Birch.%20QR-421a%20STELLAR%20results.pdf](https://www.proqr.com/files/2021-09/Euretina%20%282021%29%20DG%20Birch.%20QR-421a%20STELLAR%20results.pdf))

— **RPGR-related disease, MGT009 (Mereira/Janssen).**
MGT009 is a recombinant AAV2/5 vector designed to deliver functional copies of the open reading frame 15 (ORF15) of the RPGR gene to the subretinal space in males with XLRP. A Phase I/II trial is currently enrolling 46 patients, five years of age or older, to study the dose-escalated safety and efficacy of the
drug with an 18-month timeframe. Initial 12-month results showed that four patients in the intermediate-dose cohorts achieved clinically meaningful improvements in retinal sensitivity (1.05 dB; [90% CI: 0.81, 1.29]) and visual field progression rate (1.26 dB/ster/year; [90% CI: 0.65, 1.86]). Patients in the low- and intermediate-dose cohorts (n=6) also achieved significant improvements in their vision-guided mobility maze evaluation at low light levels with a -16.1 seconds (90% CI: 9.91, 22.1) difference between treated and untreated eyes. There were no reports of dose-limiting events, although signs of inflammation were observed in two of three patients in the high-dose cohort, successfully managed with steroids.31 The sponsor plans to dose cohort, successfully managed in two of three patients in the high-dose cohort, successfully managed with steroids.31 The sponsor plans to proceed with a Phase III trial after completing the 18-month Phase I/II trial.

— **RPGR-related disease, AGTC-501 (AGTC).** AGTC-501 is also a recombinant AAV2 vector, administered by subretinal injection in affected RPGR XLRP patients with mutations within exons 1-14 or ORF15. Thirty participants, 6 to 50 years old, were enrolled in the dose-escalation portion of the Phase I/II trial. Participation included a total of 15 visits over approximately 36 months and long-term follow-up evaluations annually for years four and five.32 Preliminary results were presented at the 2021 AAO meeting: AGTC-501 was well-tolerated across a wide dose range, with minimal adverse effects such as ocular inflammation and blurred vision. Treatment with AGTC-501 resulted in a statistically significant improvement in best-corrected visual acuity (BCVA) of ≥5 letters (9 of 13 subjects; p≤0.005). Patients were considered responders if an improvement of at least 7 decibels (dB) in at least five loci within the central 36 loci macular area (p≤0.05) was obtained by macular integrity assessment (MAIA) microperimetry. At 12 months, four out of eight patients were considered responders.33 When the Phase I/II phase is completed, a planned Phase II/III will randomize 63 participants in order to compare two doses (low and high) of AGTC-501 and an untreated control group over a 12-month time frame.

### Pre-clinical studies have shown advantageous effects of stem cell treatment, such as replacing damaged cells, adding nutritional support to remaining functioning cells, protecting retinal vascularity and promoting synaptic connections.

### Optogenetics. This is an emerging technology that employs optimized opsins, light-sensitive proteins that can modulate neural activity in retinal cells, using existing neural synapses to act as artificial photoreceptors.34 Opin genes, such as channel-rhodopsin, can be transfected into non-photoreceptor cells, such as retinal ganglion cells, through commonly used vectors, such as AAV, via subretinal injection. Four companies (Allergan, Gensight, Nanoscope Therapeutics and Bionic Sight) are actively recruiting patients for Phase I/II clinical trials to study their respective vectors’ safety and efficacy profiles. Gensight’s trial will test the combined intervention of their GS030A vector, injected into the worse-seeing eye, and a pair of specialized light-stimulating glasses (GS030-Medical Device) tasked with amplifying external visual stimuli to the transfected retina.35 Recently, Nanoscope Therapeutics shared results for its Phase I trial evaluating the safety and efficacy of MCO-010, an AAV2 vector containing multi-characteristic opsin (MCO) that doesn’t need a combination of implants or goggles, in patients with advanced disease. The results showed that six out of seven (86 percent) high-dose (3.5 × 1011 VG/eye) MCO-therapy subjects gained >0.3 logMAR (15 letters) at 52 weeks.36 The sponsor is currently recruiting patients for its randomized, double-masked Phase II RESTORE trial to assess the efficacy and safety profiles of the therapy with a timeframe of one year.37 Trials for optogenetics are all still in the early stages, with reports for only a limited number of treated patients available. Thus, future studies will help substantiate their safety and efficacy in treating RP.

### Stem cell therapy. Several types of stem cells, such as retinal progenitor, embryonic, induced pluripotent and mesenchymal, are being studied as a potential treatment modality in retinal dystrophies. Pre-clinical studies have shown advantageous effects of stem cell treatment, such as replacing damaged cells, adding nutritional support to remaining functioning cells, protecting retinal vascularity and promoting synaptic connections.38 It’s important to consider that each type of stem cell has a unique set of advantages and disadvantages.

Multiple clinical trials evaluating the safety and efficacy of stem cell therapy from various countries have had varying results.38 Currently, several clinical trials in the United States, sponsored by companies and institutions such as jCyte, ReNeuron, Cedars Sinai Medical Center and UC Davis, are holding trials to assess the use of human retinal progenitor, neural progenitor and mesenchymal stem cells, respectively, for the treatment of RP.

One sponsor, jCyte, reported the results of its Phase Ib randomized trial evaluating the efficacy of intravitreal administration of a 2-milion to 6-million-cell dose of its allogeneic human retinal progenitor cell (hRPCs) therapy, jCell, in 74 patients with RP.39 Results presented at the AAO 2021 meeting showed that patients with a central
Power and Simplicity of ROCK Inhibition

Consistent IOP reduction, whether added to a PGA monotherapy or to a combination of therapies\textsuperscript{1,2} 
Only Rocklatan\textsuperscript{\textregistered} demonstrated superior efficacy over latanoprost in registration trials at all time points\textsuperscript{3,4}

IMPORTANT SAFETY INFORMATION FOR RHOPRESSA\textsuperscript{\textregistered}

WARNINGS AND PRECAUTIONS
Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been previously contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Contact Lenses: Contact lenses should be removed prior to instillation of Rhopressa\textsuperscript{\textregistered} and may be reinserted 15 minutes following its administration.

IMPORTANT SAFETY INFORMATION FOR ROCKLATAN\textsuperscript{\textregistered}

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
• Pigmentation changes
• Eyelash changes
• Intraocular inflammation
• Macular edema
• Herpetic keratitis
• Bacterial keratitis
• Contact lens wear

Visit DISCOVaerieLive.com to learn more about these innovative IOP-lowering treatments

Please refer to Brief Summary on the reverse side.

IOP, intraocular pressure; PGA, prostaglandin analog.
**Warnings and Precautions**

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

**Use With Contact Lenses**

Rhopressa® contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of Rhopressa® and may be reinserted 15 minutes after administration.

**Adverse Reactions**

**Clinical Trials Experience**

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

The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa® dosed once daily was conjunctival hyperemia which was reported in 58% of patients. Six percent of patients discontinued therapy due to conjunctival hyperemia. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, conjunctival hemorrhage, instillation site erythema, conjunctival hyperemia, blepharitis, and conjunctival crusting.

**Herpes simplex keratitis**

Reactivation of herpetic keratitis has been reported during treatment with latanoprost. Rocklatan® should be used with caution in patients with a history of herpetic keratitis. Rocklatan® should be avoided in cases of active herpes simplex keratitis because it may exacerbate inflammation.

**Bacterial Keratitis**

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

**Use With Contact Lenses**

Contact lenses should be removed prior to the administration of Rocklatan® and may be reinserted 15 minutes after administration.

**Adverse Reactions**

**Clinical Trials Experience**

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

**Rocklatan®**

The most common ocular adverse reaction observed in controlled clinical studies with Rocklatan® was conjunctival hyperemia which was reported in 59% of patients. Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions reported were instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (1%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Other adverse reactions that have been reported with the individual components and not listed above include:

- **Netsudil 0.02%**
  - Instillation site erythema, conjunctival hyperemia.

- **Latanoprost 0.005%**
  - Foreign body sensation, punctate keratitis.

- **Rocklatan®**
  - Conjunctival hyperemia.

**Drug Interactions**

In vitro drug interaction studies have shown that precipitation can occur when eye drops containing timolol are mixed with Rocklatan®. If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution 0.005% is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

For additional information, refer to the full prescribing information at Rocklatan.com. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

**References**


Rhopressa® is a registered trademark of Aerie Pharmaceuticals, Inc. Rocklatan® is a registered trademark of Aerie Pharmaceuticals, Inc. ©2020 Aerie Pharmaceuticals, Inc. All rights reserved. US-RHO-P-0268 06/20.

**Manufactured for:** Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.
VF diameter >20 degrees had a significant improvement in visual function as measured by the primary endpoint (BCVA), which changed from baseline by 15.6 letters above sham (p=0.029). Differences between jCell and sham treatment groups were also found in secondary endpoints such as contrast sensitivity (CS): +242 percent; kinetic visual field (KVF): +317 percent; and the low luminance mobility test (LLMT): +1 Critical Illumination Level. The presentation highlighted the dependence of cone photoreceptors on the rod-derived cone viability factor (RdCVF), released by rod photoreceptors, which results in patients with more surviving adjacent rod photoreceptors having a far greater potential for restoration of cone photoreceptor function. Adverse events were generally minor and transient with only one serious Grade 3 adverse event (ocular hypertension) in the 3.0x10^6 hRPC during the 12-month study period.40

**Future Directions**

Gene editing employing the CRISPR/Cas9 system is an emerging approach for future therapies for IRDs. In brief, the CRISPR system acts as molecular scissors that cut out a portion of the damaged gene and replace it with a wild-type sequence. Results of in vitro retinal cell and in vivo mouse studies are promising, showing a slowed progression of RP.41

Recently, EDITAS Medicine released initial results from its ongoing BRILLIANCE trial for the safety and efficacy parameters of their EDIT-101 therapy to treat CEP290-related Leber congenital amaurosis. After an initial 15-month period, results showed a satisfactory safety profile with no drug-related toxicities. Two out of five patients in the medium-dose cohort saw improvement in secondary endpoints such as BCVA, FST, and mobility navigation.42 This method can be explored in the treatment of many other inherited retinal diseases if studies continue to produce favorable safety and efficacy results.

In conclusion, retinitis pigmentosa remains a leading cause of hereditary visual impairment. Diagnosis is made through a combination of clinical symptoms, diagnostic and functional assessments, and genetic testing. While treatments remain elusive, extensive research, including late-phase therapeutic clinical trials involving genetic and stem cell approaches, is under way. Initial results are promising, and we anticipate significant progress will be made in the coming years.43
Fixed-combination Compounded Therapies

Pharmacy-made drops can be an affordable and beneficial option for many of our patients.

ROMA PATEL, MD, MBA
HOUSTON

As doctors, we have many resources available to help our patients. However, some of those resources are underutilized simply because of a lack of awareness or an understanding of their advantages. Ocular therapies created by a compounding pharmacy may fall into this category for many of our peers.

The fact that fixed-combination drugs can be advantageous for our glaucoma patients isn’t a secret. However, we may be unaware of the value of the option of compounding pharmacies dispensing preservative-free drops (single-drug or fixed-combination) for some patients. I’ve found this option to provide significant benefits for many of my patients, with an easy implementation process.

Here, I’d like to review the many ways in which these compounded, fixed-combination drops have helped our patients achieve good outcomes with the potential benefits of lower cost, increased compliance and minimal time and effort for acquisition.

Making Treatment Manageable
As ophthalmologists, we likely prescribe the traditional combination medications often. But many ophthalmologists seem to be unaware that compounding pharmacies can make new combinations for us, or create preservative-free versions of the familiar combination drops, all at a very reasonable cost to our patients.

I care about this topic because many of my patients have difficulty managing regimens involving multiple drops. Barriers include physical difficulty with administration and difficulty with bottle identification or following regimens. Many of our patients or their caregivers simply don’t wait the recommended time between consecutive medication applications. Furthermore, the copay burden for our patients is ever-increasing. One of my Medicare-covered patients recently told me he pays $300 a month for his glaucoma drops—and none of them were preservative-free! There has to be a better way.

The unfortunate reality is that there’s tremendous variability regarding whether traditional combination medications will be covered by a given insurance policy. They may or may not be on-formulary, and there’s a lot of paperwork at our end to get prior authorization. In contrast, the kind of “out-of-the-box” menu offered by some compounding pharmacies can be a fruitful alternative, saving both the doctor and patient time.

In the past year, I’ve been increasingly using compounding pharmacies because of the aforementioned benefits. The companies also provide excellent customer service, especially in terms of ordering and shipping them to patients in a timely manner. In addition, many of these options are surprisingly affordable. Some of the preservative-free single agents cost about $20 a month—in some cases, $20 for a two-month supply. The savings are even more notable with some of the combination drops.

Of course, combination drops are advantageous by their very nature. Benefits include:

• Reducing or eliminating the confusion associated with a complex regimen. There’s no mystery regarding why combination drops help reduce patient confusion. Patients who have multiple bottles that need to be administered at various frequencies throughout the day often use their medications incorrectly. Studies have shown that compliance starts to decrease after adding a second agent—much less a third or fourth. For example, a patient might mistakenly take a medication twice a day that’s only supposed to be taken at bedtime. A mistake like that could actually cause an increase in the patient’s IOP. By simplifying a patient’s regimen with combination drops, we can hopefully improve adherence and potentially reduce unwanted side effects.

• Reducing side effects associated with preservatives, including ocular surface damage. Numerous studies have documented the long-term negative effects of the preservatives used in our medications, such as...
being toxic to the ocular surface. A recent article in *Nature*, published in July 2021, showed that these preservatives—the most common one being BAK—cause cytotoxic damage to both the conjunctiva and corneal epithelial cells. As a result, many of these patients have increasing signs and symptoms of ocular surface disease, such as dry eye and ocular irritation. Giving the patient combination drops is one way to minimize this problem. (It’s true that preservative-free formulations of some brand-name drops are currently available, but they’re either more expensive than those created by a compounding pharmacy or they require prior authorization from insurance companies.)

- **Convenience.** The fact that these companies mail the drops directly to the home via express shipping is very convenient for our older patients who are trying to avoid in-person interactions. (This has been especially helpful during the pandemic.) Secondly, my patients report great customer service.

- **Cost savings, even compared to generics.** Generic alternatives to branded medications used to be seen as a way to save patients money, but that advantage has diminished dramatically. Generic drug prices have quadrupled in the past 10 years. Combination drops made by compounding pharmacies are often significantly less expensive than generic drops.

One of my patients, currently managed on four therapeutics, is visually challenged, physically challenged, unable to get to the pharmacy and unable to manage three or four different bottles. I recently prescribed a combination drop that replaced three of the patient’s topical medications, and it only cost $40 for a three-month supply. This was a huge savings for the patient, and it was delivered to the patient’s home via Express Mail. For the patient, this was a lifesaver.

Why not prescribe the compounded preservative-free option? Many patients are uninsured or underinsured. This gives them a less-expensive alternative.

**Sterility**

Of course, medications must be managed somewhat differently when preservatives are omitted from the formula. The preservatives generally serve two purposes: maintaining sterility and preserving the shelf life of the medication. Preservative-free prescriptions coming from compounding pharmacies have a more limited shelf life.

In some cases, there have been sterility concerns with compounded medications such as avastin, bevacizumab and moxifloxacin, resulting in a few product recalls and advisories. But it’s important to note that these are medications that are used intraocularly. In the case of an externally applied glaucoma medication, one could say that the risk of harm to the patient—from a limited-use bottle that wasn’t thrown away at the appropriate interval—is considerably lower, but still exists.

Of course, that doesn’t change the reality that it’s of paramount importance to get patients to follow the rules. They need to understand that they can’t keep using the same unpreserved bottle for a year.

**503A vs. 503B Pharmacies**

There are two ways to make compounded pharmaceuticals, which is reflected in the two types of compounding pharmacies allowed by the FDA—503A pharmacies and 503B pharmacies. Both types of compounding pharmacies use bulk active and inactive substances obtained from FDA-registered manufacturers to create the combination drops.

A 503A compounding pharmacy can create a single, small batch of a compounded product for a single patient (for example, a single tube of a special dermatology cream to treat a rash). The formulation isn’t created until a physician issues a prescription for it. A 503A pharmacy isn’t allowed to make drugs in batches; its interactions are with a patient, not an office. Environmental monitoring must be performed every six months.

On the other hand, a 503B compounding pharmacy is an FDA-registered outsourcing facility that can provide bulk compounding. Its products can be created in larger batches, with or without an individual prescription. These facilities are required to maintain full compliance with current good manufacturing practices (CGMP). 503B facilities must produce multiple batches and submit them for testing and stability before a new product can be brought to market, which may result in longer relative lead times.

503B products and testing methods must be validated according to USP; similarly, all suppliers and vendors providing raw materials must be vetted. On-site inspections must be performed by quality personnel. An Environmental Monitoring program

<table>
<thead>
<tr>
<th>Company</th>
<th>Brand name</th>
<th>Generic name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerie Pharmaceuticals</td>
<td>Rocklatan</td>
<td>Netarsudil and latanoprost ophthalmic solution 0.02%/0.005%</td>
<td></td>
</tr>
<tr>
<td>Akorn</td>
<td>Cosopt</td>
<td>Dorzolomide HCl and timolol maleate</td>
<td></td>
</tr>
<tr>
<td>Akorn</td>
<td>Cosopt PF</td>
<td>Dorzolomide HCl and timolol maleate</td>
<td></td>
</tr>
<tr>
<td>Allergan</td>
<td>Combigan</td>
<td>Brimonidine tartrate and timolol maleate ophthalmic solution 0.2%/0.5%</td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td>Simbrinza</td>
<td>Brinzolamide and brimonidine tartrate 1%/0.2%</td>
<td></td>
</tr>
</tbody>
</table>
must be developed and performed—at minimum weekly, but usually more often.2,3

Of course, you can argue that there are reasons to be cautious about the use of compounding pharmaceuticals. FDA-approved, commercially marketed medications are subjected to more stringent quality standards than compounding pharmacies. Commercial manufacturers are required to prove the efficacy of the product. For example; before the FDA approves a marketed product, it has to undergo three sets of randomized controlled trials and studies of adverse events. Those studies have to demonstrate that the product is safe and effective and will last a certain length of time on the shelf.

Compounded products don’t have to go through that process. The pharmacies simply refer to the literature and use the same dosage of the key ingredients to make the product. (Furthermore, compounding pharmacies can create combinations that were never specifically FDA-approved as a product formulation.) Nevertheless, a 503B pharmacy is FDA-registered, which means the facility has been inspected and is considered safe for creating medication in bulk. In addition, the pharmacy has to comply with certain manufacturing guidelines, and it has to test every batch for endotoxins, sterility and potency. Since compounded solutions are required to be identical to the branded medication—and nearly identical in the case of suspensions—the likelihood of a problem with lower risk medications is remote.

Evidence of Efficacy
To demonstrate the efficacy and safety of their products, some companies have performed randomized, prospective trials. These tend to be small studies, and come with the caveat that the company is performing the study. Nevertheless, they can provide some evidence (along with our own in-clinic experience) that the compounded products do what they’re expected to do.

Patients to whom I offer these prescriptions constitute a fairly small segment of my practice ... only about 5 percent. But for that subset of patients, these can be a lifesaver.

For example, OSRX—a 503A compounding pharmacy and one of the two most widely used compounding pharmacies for ophthalmic products—conducted a proof-of-concept trial for their OMNI combination glaucoma drops, to demonstrate that these drops are as effective as individual drops used together. OSRX’s OMNI drops come in three formulas: 1) a combination of timolol and latanoprost; 2) a combination of timolol, brimonidine and dorzolamide, which they call their “A.M. Formula,”; and 3) their “P.M. Formula,” combining timolol, brimonidine, dorzolamide and latanoprost. OSRX conducted a prospective, randomized, investigator-masked multicenter study of 58 subjects with primary open-angle glaucoma who were already using at least three glaucoma drops.4 Twenty-eight of the subjects were switched to the A.M. or P.M. formula, depending on which one most closely resembled their pre-existing regimen. Over the course of 90 days, those who switched to one of the combination formulas demonstrated better IOP control and greater IOP reduction. Admittedly, this study isn’t very strong scientifically, as there are many confounding variables involved. For example, assuming that we accept the results, were they due to improved compliance or the elimination of the washout effect when multiple drops are applied too quickly in succession? The study wasn’t as clean as I’d like, but their combination drops certainly didn’t prove to be inferior to the patients’ multi-drop regimen.

My own clinical experience has largely been with the combination products produced by the other widely used compounding pharmacy: Imprimis. (I have no financial ties to either company.) I use the Imprimis drops because they offer six different combination glaucoma drops. Also, Imprimis is a 503B compounding pharmacy with the previously mentioned higher safety standards. As a result, whatever mixture of drops your patient is on, you can usually find a combination...
iCare COMPASS

The active Retinal Tracker of iCare COMPASS compensates for eye movements resulting in superior repeatability. Defects are delineated precisely. Retinal sensitivity and structure are correlated.

Discover iCare COMPASS!
+ No trial lenses
+ Patient can blink and rest without data loss
+ Easy to clean between patients

iCare HOME

24-hour at home tonometry

+ Provides an extensive view of patients IOP
+ Supports customization of individual management plans
+ Beneficial before and after glaucoma treatments

For more information, scan, call 888.422.7313, or email infoUSA@icare-world.com
www.icare-world.com/USA

For better perception
If a patient is on preservative-free compounded medications, that’s not an option.

If you haven’t tried this prescription alternative, but you’re interested in trying it, I’d suggest visiting the companies’ websites. Get familiar with the products they offer. Then, try them out on a couple of your tech-savvy patients and see what their experience is like.

Doing this is extremely easy from a prescribing standpoint. The Imprimis pharmacy, for example, is loaded in our electronic health records system, making it easy for me to order their drops electronically. If you have questions, you can call the companies’ customer service lines, and they’ll send you materials such as their catalogs, as well as patient advice cards, explaining how to interact with their system.

Patients to whom I offer these prescriptions constitute a fairly small segment of my practice. Of the prescriptions I write, compounded, preservative-free formulations only make up about 5 percent. But for that subset of patients, these can be a lifesaver.

5. Source: imprimisrx.com/assets/Ophth_Catalog_D.pdf
KEEP UP WITH CUTTING-EDGE SCIENCE IN RETINA

Retina Specialist focuses on the latest advances in the diagnosis, medical management and surgical treatment of diseases of the retina, along with practical, real-world advice from leading clinicians and other experts on managing the successful retina practice.

Watch for issues in:

- JANUARY/FEBRUARY
- MARCH/APRIL
- MAY/JUNE
- JULY/AUGUST
- SEPTEMBER/OCTOBER
- NOVEMBER/DECEMBER

FOR INQUIRIES CONTACT
RETINASPECIALIST@JOBSON.COM

WEBSITE
RETINA-SPECIALIST.COM

RETINA ONLINE

Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

ADVERTISING OPPORTUNITIES
MICHAEL HOSTER • PUBLISHER • 610-492-1028 • MHOSTER@JOBSON.COM
MICHELE BARRETT • 215-519-1414 • MBARRETT@JOBSON.COM
JONATHAN DARDINE • 610-492-1030 • JDARDINE@JOBSON.COM

FOLLOW US
@RetSpecMag
RetinaSpecialistMag
AI May Give Cataract Surgeons an Edge

In a new cross-sectional study published in *JAMA Ophthalmology*, researchers posed the question: can real-time surgical guidance for cataract surgery be achieved using a deep learning detection network combined with computer vision tools? The short answer: yes, it can. Computer vision is a newer approach to AI that allows an automated processing system to “see” the visual world and react accordingly.

In the study, researchers used a region-based convolutional neural network to track the pupil and identify the current surgical phase being performed with a mean area under the curve greater than 95%, triggering surgical guidance tools developed with computer vision.

The investigators say that the results suggest that an AI-based surgical guidance platform has the potential to enhance the surgeon experience in phaco.

Here are some of the key findings:

- The system was able to perform precise pupil tracking and segmentation as well as surgical phase identification in real time during phaco.
- Computer-vision tools were able to use the information retrieved by neural networks with the potential to share surgical data, particularly labor-intensive, expert-annotated data, is an important challenge that will need to be addressed,” Drs. Yuan and Lee note.

Sources of evidence included a sensitive search strategy in Embase, Google Scholar and hand-searching on 165 websites. Researchers extracted information from each CPG with a previously piloted sheet. Two independent authors applied the Appraisal of Guidelines, Research and Evaluation tool (AGREE-II) assessment for each CPG.

Here are some of the findings:

- Twenty-one sources including CPGs recommended anti-VEGF for DME, with wide variation among the clinical aspects included, such as location of DME, visual acuity required, and therapeutic alternatives or discontinuation.
- Most had a poor quality of reporting based on the AGREE-II tool assessment, especially those developed by ophthalmological societies, those that had exclusive content about DME, and those in which most authors disclosed conflict of interests with pharmaceutical industry or where the authors didn’t report COIs.
- Pharmaceutical-sponsored CPGs didn’t use systematic reviews to support their recommendations.
- Very few recommendations considered patient values and preferences, equity, acceptability and feasibility of the intervention.

Researchers determined that most of the clinical practice guidelines that made recommendations of anti-VEGF for DME had poor quality of reporting, didn’t use systematic reviews and didn’t consider patients’ values and preferences.

**Reviewing Practice Guidelines in DME**

Researchers identified diabetic macular edema clinical practice guidelines that made anti-VEGF treatment recommendations, and assessed their reporting quality and their considerations when making recommendations. Eligibility criteria included CPGs published between December 2009 and December 2019 that made explicit anti-VEGF recommendations in DME.

Sources of evidence included a sensitive search strategy in Embase, Google Scholar and hand-searching on 165 websites. Researchers extracted information from each CPG with a previously piloted sheet. Two independent authors applied the Appraisal of Guidelines, Research and Evaluation tool (AGREE-II) assessment for each CPG.

Here are some of the findings:

- Twenty-one sources including CPGs recommended anti-VEGF for DME, with wide variation among the clinical aspects included, such as location of DME, visual acuity required, and therapeutic alternatives or discontinuation.
- Most had a poor quality of reporting based on the AGREE-II tool assessment, especially those developed by ophthalmological societies, those that had exclusive content about DME, and those in which most authors disclosed conflict of interests with pharmaceutical industry or where the authors didn’t report COIs.
- Pharmaceutical-sponsored CPGs didn’t use systematic reviews to support their recommendations.
- Very few recommendations considered patient values and preferences, equity, acceptability and feasibility of the intervention.

Researchers determined that most of the clinical practice guidelines that made recommendations of anti-VEGF for DME had poor quality of reporting, didn’t use systematic reviews and didn’t consider patients’ values and preferences.

**Outcomes in Neuropathic Ocular Pain Therapy**

Recently, a team of researchers...
I am happy to announce an exciting addition as we continue into our seventh year of Mackool Online CME. This year, with the generous support of several ophthalmic companies, my son Dr. RJ Mackool and I will share the honor of presenting our surgical cases to you. Together we will continue to demonstrate the technologies and techniques that we find to be most valuable to our patients, and that we hope are helpful to many of our colleagues.

I will continue to narrate all of the cases, even as we share the surgical duties and thereby expand the variety of the cases that we bring to you. As before, one new surgical video will be released monthly, allowing our colleagues the opportunity to earn CME credits or just observe the case. New viewers are able to obtain additional CME credit by reviewing previous videos that are located in our archives.

I thank the many surgeons who have told us that they have found our CME program to be valuable and instructive; I appreciate your comments, suggestions and questions. Thanks again for joining us on Mackool Online CME.

Richard J. Mackool, MD
MackoolOnlineCME.com MONTHLY Video Series

**Episode 74:**
“Late Dislocation of a Sutured PMMA IOL”
Surgical Video by: Richard J. Mackool, MD

**Video Overview:**
A patient with Marfan’s syndrome and late posterior dislocation of a sutured single piece PMMA IOL is presented. Methods to reposition and resuture the IOL to the sclera are demonstrated.

**CME Accredited Surgical Training Videos Now Available Online: 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.

**Learning Objective**
After completion of this educational activity, participants should be able to:
• provide information regarding dislocation of a scleral fixated/sutured IOL
• perform methods to reattach the IOL to the sclera

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

**Accreditation Statement** - In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Review Education Group. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians (ACCME) Credit Designation - Amedco LLC designates this enduring material activity for a maximum of .25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Supported by: Glaukos, Alcon, Sony Healthcare Solutions**

**In Kind Support:**
Sony Healthcare Solutions

**Video and Web Production by:**
JR Snowdon, Inc
performed a study to more clearly determine the clinical responses to common treatment modalities in patients with neuropathic ocular pain.

The study included 101 patients with a clinical diagnosis of neuropathic pain who were seen at the University of Miami Oculofacial Pain Clinic between January 2015 and August 2021. Data from medical records including comorbid conditions and information on current or previous medication use or treatments was collected for each patient. The cohort was divided into the following subcategories based on the type of pain:

- **Post-surgical:** pain that developed after undergoing surgery (e.g., refractive or cataract);
- **Post-traumatic:** pain that followed a non-surgical trauma such as chemotherapy, radiation or brain injury;
- **Migraine-like:** bilateral pain that started spontaneously and was accompanied by photophobia and, typically in this cohort, migraine or headache; and
- **Unilateral:** pain that started spontaneously, did not follow surgery, was not typical for trigeminal neuralgia and had neuropathic qualities.

There were various treatment modalities used among the study population. The researchers wrote, “The most common oral medications were α2β ligands (48.5 percent), nonsteroidal anti-inflammatory drugs (31.7 percent) and serotonin-norepinephrine re-uptake inhibitors (16.8 percent). Oral medications were commonly paired with topical therapy, such as autologous serum tears (20.8 percent) and/or a topical anti-inflammatory (e.g., topical steroid [19.8 percent], cyclosporine or lifitegrast [17.8 percent] or less commonly, tacrolimus [8.9 percent]). Finally, a minority of patients received adjuvant therapies, including trigeminal nerve stimulation (TNS, 15.8 percent), steroid/anesthetic-based periocular nerve block (24.8 percent) and/or botulinum toxin injections (10.9 percent).”

The researchers made the following conclusions from their analysis of the recorded clinical responses to each treatment method:

- At least one oral medication reduced pain to a mild degree or greater for most patients in the post-traumatic (81.2 percent), migraine-like (73 percent) and unilateral pain (72.7 percent) groups but in only 38.5 percent of the post-surgical pain patients.
- Marked improvement from treatment with oral medications was most frequently found in migraine-like patients (21.6 percent) and to a lesser degree in the other groups (post-surgical 15.4 percent, post-traumatic 12.5 percent, unilateral 0 percent).

The investigators note that topical medication subjectively improved pain in the post-traumatic (66.7 percent), migraine-like (78.6 percent) and unilateral (70 percent) groups more often than in the post-surgical group (43.7 percent). Marked improvement was also most common in migraine-like patients for this treatment (21.4 percent).

One or more adjuvants reduced pain to a mild degree or greater in the post-surgical (54.5 percent), post-traumatic (71.4 percent) and migraine-like (73 percent) groups but did so for none of patients in the unilateral group.

As is clear from the data, responses to a number of different treatment methods vary between pain subgroups.

The researchers concluded that, though treatment responses vary by individual, different trends can be observed among pain subgroups. Future studies will hopefully identify ways to pinpoint the location(s) of nervous system dysfunction to decrease reliance on a trial-and-error therapeutic approach.

**Long-term DMEK Outcomes**

Scientists evaluated clinical outcomes of patients up to 10 years after they underwent Descemet’s membrane endothelial keratoplasty, as part of a retrospective, consecutive, single-center case series.

The medical files of eyes that received DMEK between 2009 and 2012 for the treatment of endothelial dysfunction were evaluated for follow-up time and clinical outcomes. Scientists analyzed the annual exams of 66 eyes (with a minimum of eight years of follow-up) for best-corrected visual acuity, endothelial cell density (ECD) and central corneal thickness (CCT).

Here are some of the findings from the study:

- **Best-corrected visual acuity** improved from 0.55 ±0.37 logMAR (n=54) to 0.15 ±0.11 (n=47) in eyes without ocular comorbidities one year after DMEK (p<0.001) and remained stable up to 10 years after DMEK.
- **Mean endothelial cell density** in the patients decreased to 744 ±207 cells/mm² (n=39) after nine years and to 729 ±167 cells/mm² (n=21) after 10 years.
- **The average central corneal thickness** decreased from 650 ±67 μm before DMEK to 525 ±40 μm (n=56) after one year; and increased to 563 ±40 μm (n=39) after nine years and to 570 ±42 μm (n=21) after 10 years.
- **After year eight, graft failure occurred in four eyes** that required repeat DMEK after 101 to 127 months.

The researchers reported that visual acuity remained stable in spite of slowly increasing corneal thickness and diminishing endothelial cell density during the 10-year period after DMEK.

*Int Ophthalmol; Jan. 8. [Epub ahead of print]*

Weller JM, Kruse FE, Tourtas T.
A 67-year-old is referred to Wills with periocular swelling and blurry vision.

PAULINE DIMITRIEV, MD, AND JURJ BILYK, MD

Philadelphia

Presentation and Initial Work-up
A 67-year-old male presented to the Wills Eye Hospital as a referral from an otolaryngologist for evaluation of left periocular edema and blurry vision. The patient reported that for the past nine months he had been experiencing swelling around his left eye which had started to affect his vision. When he was first evaluated by his primary care physician, he was given a course of oral azithromycin with little improvement in his symptoms. He was subsequently referred to an allergist who prescribed an additional course of oral antibiotics. Due to continued symptoms, the patient was seen by a comprehensive ophthalmologist, who ordered neuroimaging, as well as an otolaryngologist because of several episodes of left epistaxis.

Upon initial evaluation, the patient had a visual acuity of 20/25 on the right and 20/30 on the left. Intraocular pressure was 10 mmHg in the right eye and 11 mmHg in the left eye. There was no relative afferent pupillary defect. Confrontational visual fields were full. Extraocular motility was full. He was noted to have proptosis on the left, measuring 4 mm by Hertel exophthalmometry. Additionally, there was periocular edema with mild erythema, but no tenderness to palpation. Posis of the left upper eyelid was noted. No lagophthalmos was observed. No masses were readily palpated. Resistance to retropulsion was increased on the left. Apart from nuclear sclerotic cataracts in both eyes, slit lamp exam was unremarkable. On fundus exam, RPE changes were noted in both eyes, but the optic nerves appeared to be healthy. Review of CT imaging at that time was notable for a multilobulated cystic mass centered around the frontal and ethmoid sinuses on the left, with erosion through the orbital roof and into the orbit laterally (Figure 1).

Medical History
Past medical history was notable for coronary artery disease status post multiple stents and four prior myocardial infarctions, atrial fibrillation requiring ablation, diabetes mellitus, hypertension and hyperlipidemia. Ocular history was notable for an eyelid cyst that was...
Magnetic resonance imaging was obtained to evaluate the skull base in more detail; the scan showed a markedly expansile lesion (4.4 x 2.3 x 3.9 cm) centered in the left frontal sinus, with erosion into the extracranial superior left orbit and left frontal extra-axial space (Figure 2). Based on the clinical and neuroimaging findings, the differential diagnosis included fungal sinusitis (especially aspergillosis), mucocele, primary paranasal sinus malignancy, metastatic disease (especially prostate carcinoma), primary orbital mass (especially lacrimal gland malignancy), and aggressive lymphoproliferative disease (diffuse large B-cell lymphoma, mantle cell lymphoma, multiple myeloma). The patient underwent functional endoscopic sinus surgery for attempted biopsy with neurosurgery and oculoplastics on standby, but multiple specimens revealed only nonspecific inflammation on frozen sections. The lesion was then approached via a lateral brow incision into the superolateral orbit. Intraoperatively, the lesion was noted to be discohesive and bled profusely. Erosion of several of the bones of the orbit was noted. Frozen sections revealed a cellular lesion consistent with neoplasia, suspicious for malignancy. Vision, pupillary examination and extraocular motility were noted to be stable postoperatively. Toward the end of the case, the anesthesia team also noted blood in the patient’s Foley bag, initially thought to be secondary to a traumatic Foley catheter insertion. A postoperative urology consultation was obtained.

Final pathology was consistent with metastatic renal cell carcinoma. The patient underwent systemic evalu-
OPHTHALMOLOGIST
Danbury, CT

Ophthalmologist to share office with long standing Ophthalmologist in Danbury, CT. High quality equipment. $1850 per month or adjoining office without equipment- $1500 per month.
203-545-3539 or 203-748-2020
e-mail mehrimmd@aol.com

Do you have Products and Services for sale?
CONTACT US TODAY
FOR CLASSIFIED ADVERTISING
Toll free: 888-498-1460
E-mail: sales@kerhgroup.com

REVIEW
Do you have Products and Services for sale?
CONTACT US TODAY
FOR CLASSIFIED ADVERTISING
Toll free: 888-498-1460
E-mail: sales@kerhgroup.com

ADVOCATE INDEX
This advertiser index is published as a convenience and not as part of the advertising contract. Every care will be taken to index correctly. No allowance will be made for errors due to spelling, incorrect page number, or failure to insert.

Advancing Eyecare ............................................................................................................................................ 51
Aerie Pharmaceuticals Corporate ......................................................................................................................... 6
Aker ................................................................. 0
Akorn ........................................................................................................................................................................ 9
Apellis .................................................................................................................................................................43
Bruder ............................................................................................................................................................... 15
Imprimis Pharmaceuticals, Inc. .........................................................................................................................17
Keeler Instruments ............................................................................................................................................. 75
Mohian Therapeutics ........................................................................................................................................ 9 & 20
Oasis .................................................................................................................................................................... 39
Regeneron Pharmaceuticals, Inc. ......................................................................................................................2 - 4
Toll free: 888-498-1460
E-mail: sales@kerhgroup.com

Contact us today
for classified advertising:
Toll free: 888-498-1460
E-mail: sales@kerhgroup.com

www.acellfx.com
www.allergan.com
www.nextgen.com/1-ophth
www.theratears.com
www.tollfree411.com
www.nanodropper.com
www.lombartinstrument.com
www.oasismedical.com
www.bruker.com
www.stephensinst.com
www.imitorc.com

www.regeneronhealthcare.com/questions
tion, including positron emission tomography, which revealed a 12-cm, hypermetabolic mass in the right kidney, as well as hypermetabolic lesions in the left frontal sinus and right proximal femur, consistent with stage 4 RCC. The patient underwent immunotherapy and palliative radiotherapy.

Discussion

Orbital tumors vary widely in their clinical, histopathologic and imaging features, as well as in their malignant potential and the tissue types from which they arise.\(^3\)\(^,\)\(^4\) Bone erosion can occur with parasinal sinus fungal infections and is a hallmark of frontal sinus mucoceles. However, primary sinus malignancy and metastatic disease also frequently present with extensive skull base bone changes.

The most common primary sites for tumors that metastasize to the orbit are breast, lung and prostate.\(^1\) Clinical presentations vary but commonly include exophthalmos, enophthalmos (in cases of scirrhous breast carcinoma), globe displacement, restriction of extraocular movements, ptosis, decreased vision and pain. Certain pathologies that affect the orbit tend be vascular and bleed extensively during surgery, including multiple myeloma; amyloidosis; and metastatic prostate, renal cell and thyroid carcinomas, as encountered in this case. Notably, these entities may also present with spontaneous bleeding and ecchymosis, narrowing the differential diagnosis for the clinician.

The incidence of RCC has been rising steadily.\(^3\)\(^-\)\(^5\) RCC is the most common malignant tumor that arises from the renal cortex. It occurs twice as frequently in men and predominantly affects individuals in their seventh and eighth decades of life. Cigarette smoking and obesity have been found to increase the risk of developing RCC. Most cases of RCC are sporadic, but some are associated with von Hippel-Lindau (VHL) disease, with 40 percent of patients with VHL disease developing RCC in their lifetime. Although classically associated with the triad of hematuria, pain and a flank mass, more than 60 percent of RCC cases are detected incidentally, and upwards of 25 percent of patients with RCC will have metastatic disease at the time of initial presentation.\(^5\) The most common sites for metastasis of RCC include the lung, brain, liver and bone. Patients with metastatic RCC have a median survival of a little over one year with a five-year survival rate of less than 10 percent.\(^3\)

In patients without metastatic disease, nephrectomy is the mainstay of treatment. In patients with metastatic disease, surgical resection is considered if it’s likely to improve quality of life by reducing bothersome symptoms; however, patients with solitary metastases at the time of presentation generally do poorly, even if both primary and metastatic sites are treated aggressively.\(^6\)

Orbital metastasis of RCC is rare, with only a few dozen cases described in the literature, likely by hematogenous spread.\(^5\)\(^,\)\(^7\) Metastatic RCC lesions tend to enhance on MRI with gadolinium.\(^8\) As in this case, orbital metastases may be the first presentation of an occult primary tumor. Other cases have been described in which metastases are delayed many years after initial diagnosis of RCC.\(^2\) Biopsy is often required to establish the diagnosis in patients with no known primary malignancy. Additional systemic evaluation with positron emission tomography/computed tomography (PET/CT) is warranted to identify other sites of metastasis.

Once diagnosed, the management of RCC with metastasis to the orbit entails a combination of surgery, radiotherapy, chemotherapy and immunotherapy. As mentioned previously, overall prognosis for patients with metastatic RCC, despite treatment, remains poor.\(^5\)\(^,\)\(^7\)

In summary, RCC metastasis to the orbit is a rare occurrence and typically presents with unilateral proptosis, pain, ptosis and occasionally decreased vision. As was the case in our patient, the metastatic lesion is often the first presentation of RCC, as the primary tumor is often indolent until later in the disease course. A multidisciplinary treatment approach is used to treat patients with metastatic RCC with the aim of minimizing symptoms and improving quality of life. Unfortunately, the prognosis for patients with metastatic RCC is poor.

As was the case in our patient, the metastatic lesion is often the first presentation of RCC, as the primary tumor is often indolent until later in the disease course.

The Vantage BIO is great for ROP screening! It’s lightweight, has settings for different pupil sizes, a cool, white LED light and the longest battery ever!!”

Dr. Paulina Ramirez Neria

I’m a big fan of the All Pupil BIO. I had issues with other models so when I started [my practice], I knew the All Pupil would be my go-to BIO…I greatly appreciate the new custom fit Keeler BIO shields as an added safety layer.”

Dr. Annie Bacon

I chose my [Vantage Plus] for the optics and value…with other brands, I had difficulty focusing up close during my dilated fundus exams. [The oculars] made my eyes feel more relaxed, and I felt like my view was better.”

Dr. Michelle Hammond

[I’ve] been seeing emergent and urgent cases every day during the COVID19 pandemic. I really like [the Vantage BIO] because [it’s a] very good quality and provides a super clear view.”

Dr. Reza Moradi

Choose option #1 or #2 below when you purchase (or lease) a BIO*

(Expires March 31, 2022)

*Valid for wireless indirects: Vantage Plus and/or All Pupil II

1. RECEIVE A $850 credit towards any PPE

2. 24-MONTH LEASE AS LOW AS $128/MONTH*

*All Pupil II: $127.92/month; Vantage Plus: $155/month (shipping and taxes not included).

3. RECEIVE 10 FREE bottles of phenylephrine 2.5%, 15mL

*If you lease the BIO, you may also choose the PPE credit OR the phenylephrine option.

Contact us at 800-523-5620 or customerservice@keelerusa.com to learn more or place your order. This promo cannot be combined with any other Keeler offers.
INDICATION FOR USE. The iStent inject® W Trabecular Micro-Bypass System Model G2-W is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma.

CONTRAINDICATIONS. The iStent inject® W is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. 

WARNINGS. Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. 

MRI INFORMATION. The iStent inject® W is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. 

PRECAUTIONS. The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent inject® W have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SJ performed > 90 days preoperatively), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents.

ADVERSE EVENTS. Common postoperative adverse events reported in the iStent inject® randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent inject® vs. 4.2% for cataract surgery only), secondary surgical intervention (6.4% vs. 5.6%) and BOS/scleral thinning >3 lines >3 months (2.6% vs. 4.2%). CAUTION: Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events. 

Glaukos®, iStent®, iStent inject®, and iStent inject® W are registered trademarks of Glaukos Corporation. All rights reserved. ©2021 PM-US-0343

POWERFUL. PREDICTABLE. PROVEN. 

Get started with micro-invasive glaucoma surgery using iStent inject® W today. Contact your local Glaukos rep for more information.