REVIEW® of Ophthalmology

January 2017

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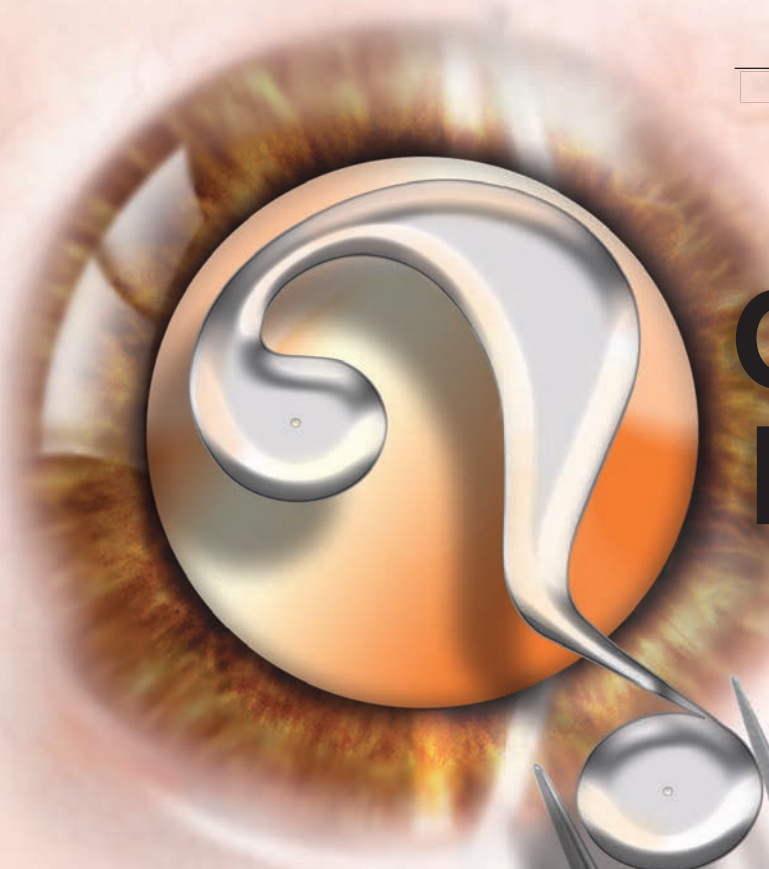
IOL ISSUE

HOW TO CHOOSE THE RIGHT LENS

Expert tips on selecting the best IOL formulas. **P. 25**



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REVIEW NEWS
Volume XXIV • No. 1 • January 2017

The Cures Act Becomes The Law of the Land

The Cures Act, formerly known as 21st Century Cures, became law in mid-December of 2016 and carries with it a lot of hope for patients suffering from a range of illnesses, as well as the potential for quicker approval of drugs and devices. It sets aside funds for the Precision Medicine Initiative for personalized medicine, the "Cancer Moonshot" research championed by Vice President Joe Biden, and the BRAIN initiative aimed at studying neurological disease. Some observers, though, are a little wary of several of the law's provisions, especially those that seem to water down the Food and Drug Administration's approval process.

One of the law's key aspects is the funding it provides to the National Institutes of Health, which would amount to $4.8 billion over 10 years. "There are a lot of things that sound good about the law," says Michael Repka, MD, the American Academy of Ophthalmology's medical director for government affairs, and a professor of ophthalmology and pediatrics at Johns Hopkins in Baltimore. "The $4.8 billion or so would be a terrific improvement in a space that's been somewhat stifled in recent years [out of] particular concern about too much spending among members of Congress and even on the executive side.

"[Another] thing that's probably good for us involves lessening EHR-blocking regulations," Dr. Repka continues. "We have had issues with IRIS registry and data blocking by certain large EMR vendors. In order for [AAO] members to be successful in the new quality payment program, particularly the [Merit-based Incentive Payment System], it's really important for us to have access there. So, we hope that will get better with this law. Specifically, many of the AAO members who aren't in the IRIS registry happen to have one of the large, institutional-based EMR's such as EPIC, which, for the most part, can't participate in the IRIS registry. Of course, participating in the IRIS registry is important because it's a relatively painless way to succeed in MIPS."

There's a chance, however, that the billions in funds might not materialize. "The biggest promise of the law—greater funding for the NIH—is a bit illusory, in that it's subject to the appropriations process each year," cautions Ameet Sarpatwari, PhD, JD, Instructor in Medicine at Harvard Medical School and assistant director of the Program on Regulation, Therapeutics, and Law at Brigham and Women's Hospital in Boston. "And, as we've seen in years past, that sort of set-aside can be raided during that process, so it's not necessarily a sure thing."

Dr. Sarpatwari goes on to outline other aspects of the law that could have some negative effects down the road depending on how they're implemented. "One concern regards supplemental approval of drugs, meaning drugs that are already on the market but are looking to gain another foothold in terms of another indication," he says. "The bill potentially lowers the bar for their approval while, at the same time, purporting not to. It essentially commands the FDA commisioner to promulgate new guidance on the use of the various ways to get a drug approved, which, in this case, is the use of real-world evidence. This provides a bit more cover to allow drugs with less-clear evidence of efficacy to go through. Essentially, it's saying, 'How can we use just regular, observational data to support a supplemental drug approval?' That's problematic because that type of evidence can be very misleading, and isn't subject to the same rigor that a randomized clinical trial is.

"The second area involves the issue of medical devices," Dr. Sapartwari continues. "There's an existing pilot program that would allow so-called breakthrough devices to be approved under a sort of accelerated time frame using, basically, more questionable evidence. What the Cures Act would do is formalize this program and expand it to potentially allow more products under it, because the products that can be classified as 'breakthrough' under this pathway don't necessarily have to be clinically meaningful. So, there's an inherent tension if you speed up the review of products and base it on less-rigorous evidence. You're going to allow more devices through that aren't, again, necessarily that effective. And, if they aren't that effective, this changes the risk/benefit profile of these products, and results in significant waste

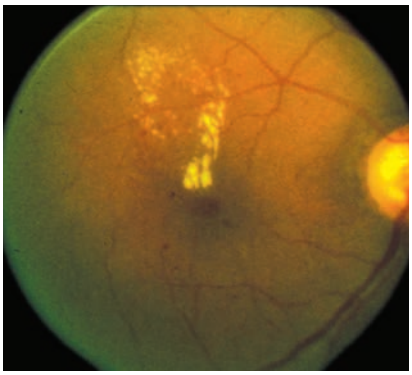
for patients and taxpayers who have to pay for them. This is important in the context that, when you look at the evidence base that supports device approvals, it is already far less than that which supports new drugs."

The third aspect that concerns some is the law's use of the limited population pathway for antibiotic approval. "This would allow antibiotics to be approved on a sliding benefit/risk scale," Dr. Sarpatwari explains. "And so, you can imagine again that it allows the FDA commissioner to use his or her discretion to steer through more products that previously wouldn't have gotten through. Then, the law would require the product to indicate that it had been approved under this limited pathway. However, we know that, based on evidence, particularly from the nutritional supplement industry, consumers don't really heed these disclaimers very well."

Dr. Repka says worries over lax approval standards have always accompanied FDA revamps. "That's always been the dilemma with the FDA," he says. "Where do you put the cut point between safety, aka patient protections, and technology advancement? That's tough to do. This seems to lean both ways: improving the support of the safety side but also helping to promote some innovation. I think that anytime the FDA gets pushed to move things along, this is going to be a very appropriate concern. In no way should we downplay that, and we should continue to say that the agency, as it implements the programs as designed, shouldn't pay short shrift to the approval process."

Google Algorithm Detects Diabetic Retinopathy

In a study sponsored by Google, researchers tested a newly developed deep learning computer algorithm designed to detect diabetic retinopathy and diabetic macular edema from retinal fundus photographs. Deep learning is a computational method which allows an algorithm to program itself through "learning." The project's system, called DeepMind, "learns" by studying a large set of examples that demonstrate the desired behavior and then adapting itself in response.



Google's learning algorithm was able to detect diabetic retinopathy with 90 percent sensitivity and 98 percent specificity.

The algorithm graded 128,175 retinal images three to seven times each for diabetic retinopathy and DME. The images were also examined by a panel of 54 U.S.-licensed ophthalmologists. When set for high specificity, in two validation sets composed of 9,963 images and 1,748 images, the algorithm had a 90.3-percent and 87-percent sensitivity and 98.1-percent and 98.5-percent specificity, respectively, for detecting referable diabetic retinopathy—which was defined as moderate or worse diabetic retinopathy—or referable macular edema by the majority decision of a panel of at least seven of the ophthalmologists. When set for high sensitivity, the algorithm had 97.5-percent and 96.1-percent sensitivity and 93.4-percent and 93.9-percent specificity, respectively, in the two validation sets.

In reviewing the data, one of the DeepMind researchers, Google's Lily Peng, MD, PhD, observes, "The results show that our algorithm's performance is on-par with that of ophthalmologists. For example, on the first validation set, the algorithm has an F-score [combined sensitivity and specificity metric] of 0.95, which is slightly better than the median F-score of 0.91 achieved by the eight ophthalmologists we consulted. The significance here is that deep-learning algorithms had high sensitivity and specificity for detecting diabetic retinopathy and diabetic macular edema in retinal fundus photographs."

With regard to the algorithm's place in a clinical setting, its practical application requires further research. "Another open question is whether the design of the user interface and the online setting for grading used by ophthalmologists has any impact on their performance relative to a clinical setting," says Dr. Peng. "Addressing this will require further experiments. The algorithm has only been trained to identify diabetic retinopathy and diabetic macular edema. It may miss non-diabetic retinopathy lesions that it was not trained to identify. Hence, this algorithm is not a replacement for a comprehensive eye exam, as it will ignore components such as visual acuity, refraction, eye pressure measurements, etc. However, with further research, the results suggest that the algorithm could lead to improved care and outcomes compared with the current ophthalmologic assessment."

Although further research is necessary, this new deep-learning algorithm has potential use in telemedicine, as it will allow patients to "self-diagnose" in the comfort of their own homes, even if it is only for diabetic retinopathy and diabetic macular edema. "Along with telemedicine, technologies such as these could increase access to care and assist in screening for diabetic retinopathy in areas with limited resources," Dr. Peng claims.

(Continued on p. 50)

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INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

- PROLENSA® contains sodium sulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
- All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Use with caution in patients who have previously exhibited sensitivities to these drugs.
- There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Use with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.
- PROLENSA® should not be instilled while wearing contact lenses. The preservative in PROLENSA®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA®.
- The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

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

References: 1. PROLENSA Prescribing Information, April 2013. **2.** Data on file, Bausch & Lomb Incorporated. **3.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of (14)C-labeled bromfenac following topical instillation into the eyes of New Zealand white rabbits. *J Ocul Pharmacol Ther.* 2008;24(4):392-398.

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PROLENSA®
(bromfenac ophthalmic solution) 0.07%

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PROLENSA® (bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

DOSAGE AND ADMINISTRATION

Recommended Dosing

One drop of PROLENSA® ophthalmic solution should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

Use with Other Topical Ophthalmic Medications

PROLENSA ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time

With some NSAIDs, including bromfenac, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that PROLENSA® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

PROLENSA should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

ADVERSE REACTIONS

Clinical Trial Experience

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

The most commonly reported adverse reactions following use of PROLENSA® ophthalmic solution following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia and vision blurred. These reactions were reported in 3 to 8% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

Treatment of rats at oral doses up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality and reduced postnatal growth at 0.9 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of PROLENSA® ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when PROLENSA is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

Geriatric Use

There is no evidence that the efficacy or safety profiles for PROLENSA differ in patients 70 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively, revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents. Advise patients that a single bottle of PROLENSA® ophthalmic solution, be used to treat only one eye.

Concomitant Use of Contact Lenses

Advise patients to remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart.

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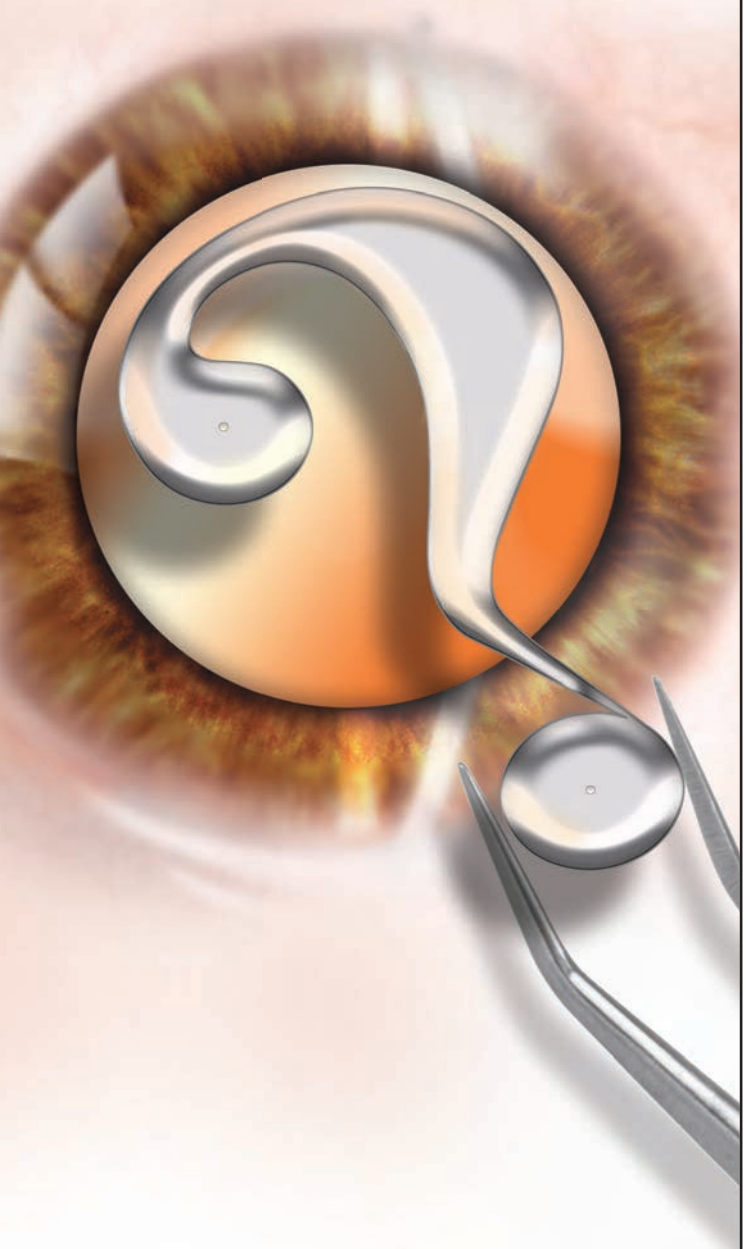

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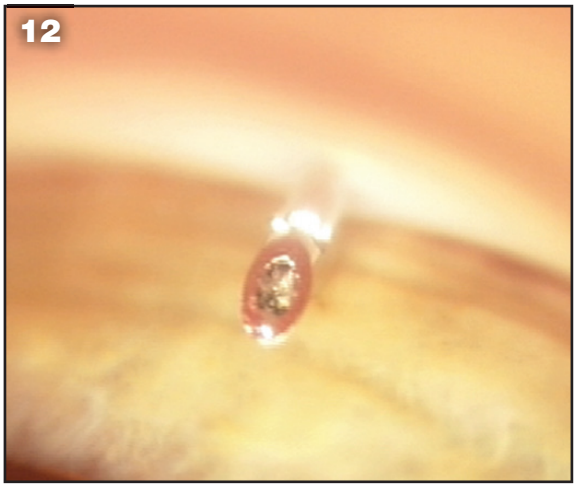

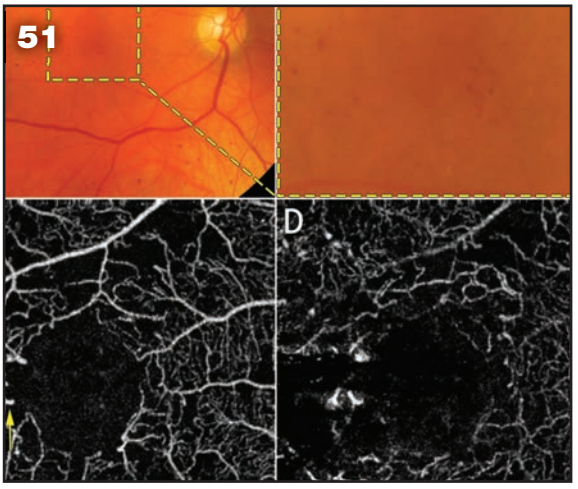

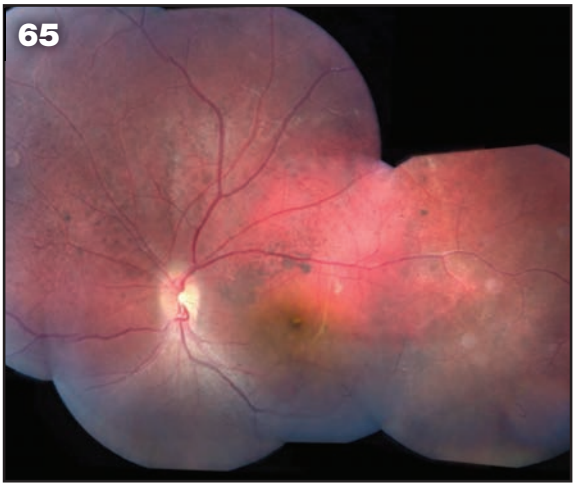

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Keeping Your Trabeculectomy On Track

With so many factors beyond our ability to control, it behooves us to be vigilant about controlling the things we can.

Thomas W. Samuelson, MD, Minneapolis

Trabeculectomy has been the primary go-to operation for surgical glaucoma care for most of my career. However, that's changed pretty significantly in the past five years or so with the advent of minimally invasive glaucoma surgeries, or MIGS. Filtration surgery is highly effective, but it isn't safe enough to justify using it to treat mild or moderate glaucoma. The MIGS procedures nicely fill that niche, so it's no surprise that they're doing well. Meanwhile, because of MIGS, we're doing far less filtration surgery than we have in the past, although admittedly we only have two or three years' follow-up on the majority of MIGS procedures completed thus far.

Although trabeculectomy is being performed less frequently, I suspect most glaucoma surgeons would agree that when a patient has very advanced, rapidly progressive glaucoma requiring a dramatic pressure reduction, filtering surgery is still the fastest way to get that patient out of trouble. Most MIGS surgeries simply don't have the pressure-lowering efficacy that a patient with advanced disease may need, and unfortunately, there's still a lot of advanced disease out there. Those of us who primarily treat glaucoma see a lot of those patients, so we're still doing quite a few filtering surgeries.

One of the primary reasons filtration surgery can produce mixed results is that there are so many uncontrollable variables in the surgery—factors that we can't predict or manipulate. For example, we can't control the integrity of the conjunctiva-Tenon's complex, especially three, four or five years after the procedure. As a result, some blebs will break down; some will leak late; and some will fibrose very rapidly and fail. On the other hand, there are plenty of things we can control, so it's important for us to be masters of those things.

Here, I'd like to discuss some of the issues surrounding filtering surgery and offer some strategies that will help produce the best possible outcomes for these patients.

Optimizing the Surgery

Intraoperative technique is one of the things within our control, and filters do sometimes fail because of poor technique. These strategies can help you avoid trouble.

- ***Before surgery, address any toxicity caused by glaucoma medications.*** Make sure the ocular surface is primed for a good surgical outcome. If the patient has a toxic surface because of aggressive medical therapy for glaucoma, pretreat the patient with steroids. If someone has follicular conjunctivitis because of an allergy to topical CAIs or brimonidine (the two most common allergies) you might want to stop the offending agent a few weeks before surgery to try to minimize inflammation on the ocular surface. Follicular conjunctivitis will doom a filter from the outset.
- ***Make sure the sclerostomy is adequate.*** A poorly executed sclerostomy will result in insufficient flow or too much flow—the latter making the patient hypotonous and problematic from the start. Experienced glaucoma surgeons respect and fear hypotony as much or more than elevated intraocular pressure.
- ***Perform meticulous wound closure.*** This is crucial for preventing perioperative wound leaks. Even with careful wound closure, small,

This article has no commercial sponsorship.

transient leaks may occasionally occur at the incision site, but significant wound leaks early in the postoperative period should be very uncommon.

It's true that we can't control late leaks, typically caused by the conjunctiva breaking down. That's partly because we have a catch-22 in glaucoma surgery: We have to use antimetabolites to prevent aggressive healing. Those antimetabolites may cause the tissue to break down over time, leaving us with problems several years down the road.

In the meantime, however, careful wound closure can prevent most immediate leaks.

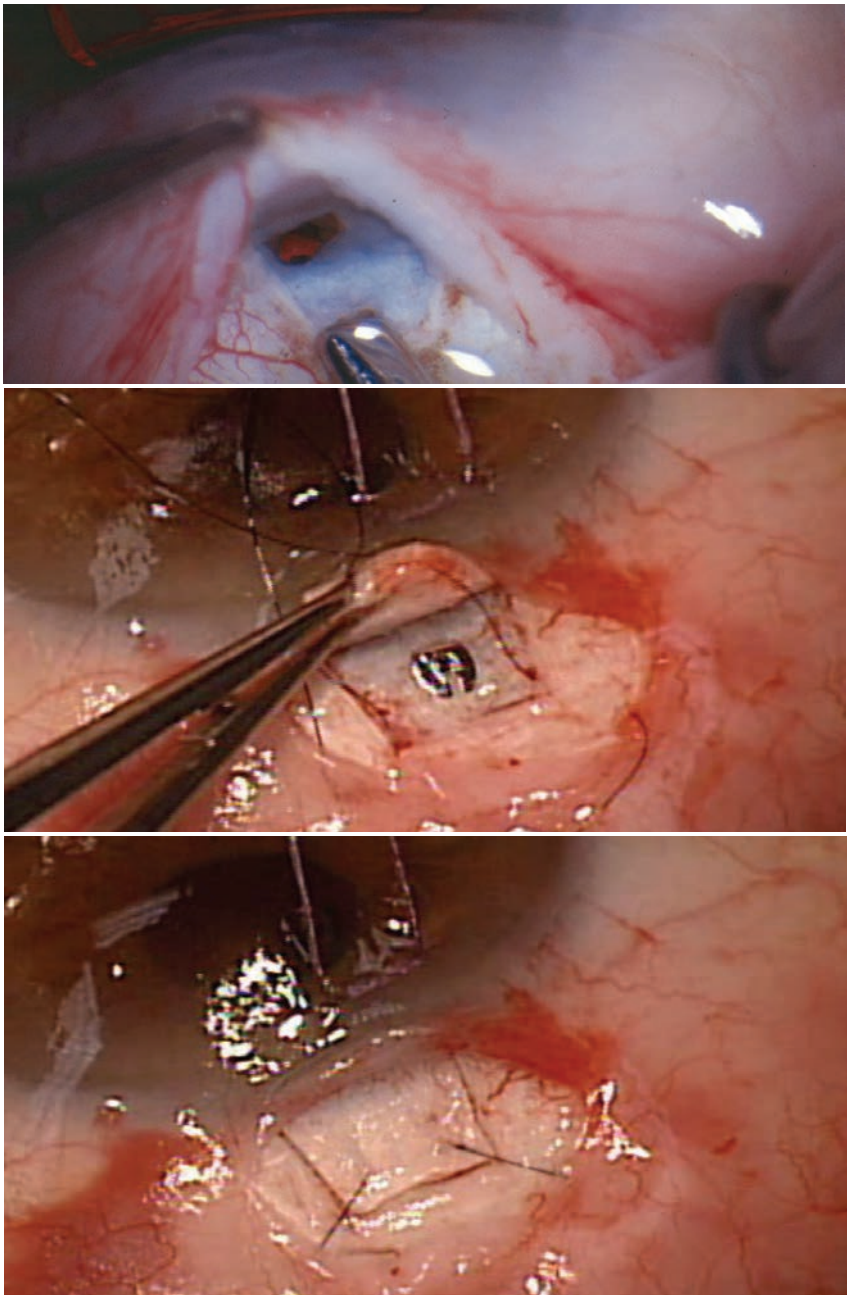
Postoperative Management

One of the nice things about trabeculectomy is that it's titratable. We establish an outflow pathway and make sure there's abundant flow; then we control that flow by how tightly we suture the scleral flap, and by suturing it in such a way that we can release the sutures later to allow additional flow as needed.

• ***Think carefully about the timing of suture release.*** When to cut or release sutures is highly dependent on the severity of the glaucoma. How vascularized is the bleb? How low is your target pressure? How advanced is the glaucoma? Is the eye phakic or pseudophakic? How much does the patient depend on the surgical eye? (For example, if the other eye has no light perception, we have to be very careful not to put central vision at risk.) All of these things should factor into how aggressive we are with our surgery and suture releasing. Because of the multiple issues involved, it takes a lot of experience and surgical wisdom to time suture lysis and release correctly.

• ***You may want less flow at one day postop than later on.*** Some patients come into glaucoma surgery on multiple medications, and much of that pharmacologic therapy was intended to reduce aqueous production. In that situation the ciliary body may have been receiving the pharmacologic message to not make aqueous for years. Now we're creating a new outflow system. If the outflow is overly aggressive and the ciliary body is still under the influence of pharmacological suppression, the result can be hypotony.

However, as the ciliary body recovers from the effect of those drugs, it will probably make more aqueous one or two weeks postop than it was making at postop day one.



Whether the sclerostomy is created manually with a blade or punch (top) or with a device (middle), filtration is controlled with sutures (bottom) that can be released or lysed to individualize care and titrate flow postoperatively.

An Early Look at the XEN Gel Stent

In late November, 2016, the U.S. Food and Drug Administration approved Allergan's XEN glaucoma implant system, comprised of the XEN45 gel stent and a proprietary injector, for commercial use. The XEN system had previously received the CE Mark and been approved in Canada, and more than 10,000 devices have been implanted worldwide. The stent is made of a soft, flexible collagen-derived gelatin that's highly biocompatible and noninflammatory; it's 6 mm long and about the width of a human hair. It's implanted using an *ab interno* approach, injected through a self-sealing corneal incision using a preloaded injector. Once in place it reduces intraocular pressure by creating a new drainage channel from the anterior chamber into the subconjunctival space, resulting in the creation of a bleb. (One advantage of this method of implantation is the preservation of external ocular tissue, allowing a greater array of future treatment options than might be available following other procedures such as a trabeculectomy or tube shunt.) The pliability of the material allows the stent to conform to the anatomy of the ocular tissue, helping to minimize issues such as migration, erosion and corneal-endothelial damage.

According to the approval, XEN is indicated for the management of refractory glaucoma where previous surgical treatment has failed, and in patients with primary open-angle glaucoma—as well as pseudoexfoliative or pigmentary glaucoma with open angles—that are unresponsive to maximum tolerated medical therapy. A clinical trial of the device involving 52 refractory glaucoma patients found that the stent reduced IOP from a mean baseline of 25.1 ±3.7 mmHg (on medications) to 15.9 ±5.2 mmHg at 12 months. Use of IOP-lowering medications dropped from 3.5 ±1 medications to an average of 1.7 ±1.5 medications.

According to the company, XEN is contraindicated in angle-closure glaucoma where the angle has not been surgically opened; when the target quadrant has previously had a glaucoma shunt, conjunctival scarring or pathology; and in the presence of active iris neovascularization, an anterior chamber intraocular lens, intraocular silicone oil or vitreous in the anterior chamber. Complications arising from implantation of the XEN stent may include choroidal effusion; hyphema; hypotony; implant migration; implant exposure; wound leak; the need for secondary surgical intervention; and intraocular surgery complications. (The safety and effectiveness of the device in neovascular, congenital and infantile glaucomas has not been established.)

The most common postoperative adverse events included a loss of two or more lines of BCVA (experienced by 15.4 percent of patients during the first month and 6.2 percent at one year); hypotony, defined as an IOP <6 mmHg, at any time (experienced by 24.6 percent of patients, although no clinically significant consequences occurred and no surgical intervention was required); an IOP increase greater than 10 mmHg from baseline (experienced by 21.5 percent of patients); and a postoperative needling procedure (performed in 32.3 percent of patients).

Davinder S. Grover, MD, MPH, attending surgeon and clinician at Glaucoma Associates of Texas in Dallas, has used the XEN implant for the past several years as part of the U.S. pivotal trial. He notes that, compared to other MIGS procedures, XEN stands out because of its ability to treat advanced glaucoma. "I think this will be a very safe and effective MIGS procedure for all types of glaucoma," he says. "That's the most powerful thing about it. I've seen the XEN used successfully on a large spectrum of patients, from mild to moderate to very advanced disease."

He notes that the way the implant procedure was done for the FDA trials is different from the way the procedure is usually performed outside the United States. "Implanting the XEN involves the use of mitomycin-C," he explains. "The FDA would only allow the company to use Mitosol, the only FDA-approved formulation of MMC. However, Mitosol is only indicated for *ab externo* use. As a result, we were required to take down the conjunctiva in order to apply MMC, then insert the device via an *ab interno* approach, and then close the conjunctiva. In addition, the FDA trials were done with advanced, refractory glaucoma cases. In contrast, the APEX trial that was done in Europe used a different study population with less-advanced glaucoma and MMC injected through the conjunctiva. That trial showed even better results. So, I'm optimistic that we'll see fewer complications and an even higher success rate once we can perform the procedure that way over here."

For more information about XEN, visit Allergan.com.

Dr. Grover is a speaker and consultant for Allergan.

—Review Staff

In these patients, the drain needs to be smaller immediately after surgery and larger at one or two weeks. Again, this is one of the advantages of doing trabeculectomy; we can titrate it as the ciliary body recovers from years of aqueous suppression.

• ***Optimize your use of postoperative steroids.*** I generally use a steroid up to four months, sometimes longer, after a typical trabeculectomy. (Note that the risk of increased IOP because of the steroid use is minimized by the bleb.) I suggest a minimum of three months for phakic eyes and four months for pseudophakic eyes. This is not because pseudophakic eyes have more inflammation, but because there's no risk of cataract formation in a pseudophakic eye.

• ***Create a good bleb at every early visit.*** I like the patient to leave each postoperative visit with a pressure of 6 to 10 mmHg. If it's postoperative day one and the pressure is 18, I'll use localized or focal massage to generate a well-formed bleb to bring the pressure down. You don't want the raw surgical surfaces, the Tenon's conjunctival complex and the sclera, to be adherent; instead, you want a cushion of aqueous between them. So I want to generate a bleb each time I see the patient. If I find that I still have to do focal massage at each visit in the second or third week postop, I'll

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INDICATIONS AND USAGE

OMIDRIA is added to ophthalmic irrigation solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2015.

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cut a suture to increase the outflow.

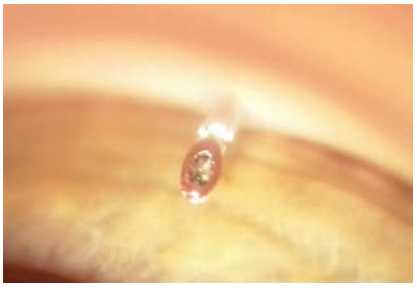
• ***Be alert for bleb leaks.*** Leaks are bleb killers. If it's a significant leak and the bleb is flat, do something to seal the leak so the bleb is regenerated. If the bleb has been flat for a while postoperatively, it's going to fail because there's no potential space there. The conjunctiva will scar down and when the leak eventually seals, the potential subconjunctival reservoir has scarred down. So, fix leaks as quickly as possible to maintain the bleb.

• ***If all sutures have been cut and the pressure is still too high, use gonioscopy to see if the sclerostomy is patent internally.*** If you find that the sclerostomy is not patent internally, take measures to clear the sclerostomy, such as YAG or argon laser iridoplasty.

• ***If all sutures have been cut and the pressure's still too high, consider needling the bleb.*** Needling may help to salvage a bleb that's threatening to fail early on. In many instances needling can prevent the patient from having to go back on medications.

Before needling the bleb, pretreat with neosynephrine to blanche blood vessels and minimize bleeding. Then, take a needle and probe under the bleb and/or scleral flap to see if you can reestablish flow. If flow is reestablished, I may bring the patient back in several days or a week later to repeat the needling, this time administering antimetabolites. If I'm unable to reestablish flow, I'll have the patient resume medical therapy.

• ***If you use an ExPress shunt and the bleb fails, occlusion of the shunt could be the cause.*** I sometimes use Alcon's ExPress shunt for filtering surgery; it helps me achieve very reproducible results, since the outflow channel is consistent. I find the ExPress especially useful in more elderly patients, or in individuals on anticoagulants. The downside is that



Gonioscopic view of an ExPress implant with an obstructed ostium prior to applying YAG laser energy to re-establish flow.

it adds one more consideration if the bleb fails, because it's possible that the device has become occluded with fibrin or inflammatory material. For this reason, I tend to not use an ExPress shunt in younger individuals or those prone to inflammation.

If the bleb does fail after implanting an ExPress shunt, it can be difficult to tell whether an occlusion is the source of the bleb failure. I've had several patients who maintained excellent pressure with the ExPress for several years; then they suddenly came in with high pressure. In this situation my first strategy is to needle the bleb. If that has no effect, I take them to the YAG laser and fire 2 to 6 mJ of energy up the lumen of the shunt; this frequently causes the pressure to drop dramatically. If that happens, I'll treat the patient with an ongoing topical steroid to keep the blockage from recurring.

For some surgeons the possibility of an occlusion is reason enough not to use an ExPress device. They'll say, "I don't want to add one more thing that could go wrong." But for some patients the intraoperative control and precision the ExPress offers is worth the small risk of occlusion.

• ***Don't skimp on follow-up visits.*** Make sure you see the patient in a timely manner. This isn't "cut and forget" surgery; it requires careful postoperative monitoring. The reason this can be a challenge is that postoperative care is a lot of work, and it's not reimbursed. To put it another way, the reimbursement is the same whether you see the patient five times or 20 times. It's difficult to fill your clinic up with nonreimbursed visits, but it's important to see these patients regularly to help ensure the best possible outcome. You just have to accept that it's a lot of work.

Communication Counts

A good outcome often depends on getting patients—and in some cases referring doctors—to understand what needs to be done to minimize postoperative risks.

• ***Do what you can to make sure patients return in a timely manner.*** It's not easy to convince patients that it's important for them to come back weekly for the first few weeks; they may, for example, be dependent on a family member for a ride. It's worth spending a little time to make sure the patient understands how important these visits are.

• ***Educate patients that they must always be alert for long-term complications, even though the risk is low.*** Patients are never completely out of the woods with filtration surgery; they can still have problems five or 10 years later. For that reason it's important to educate them about that possibility. I always tell patients who have highly functional, pale, ischemic blebs that if aqueous can get out of the eye, bacteria can get in. That makes it critical for patients to take precautions against infection and understand the symptoms of infection. They need to be ready to take action if their eye gets red or they get a purulent discharge. In that situation they should be started on antibiotics immediately.

Some of my patients travel to third world countries or go to Mexico for spring break, and they can find themselves in situations where they can't get medical care promptly.

When I'm aware of such travel, I make sure these patients take a fourth-generation fluoroquinolone along with them on the trip. That way, if they develop a red eye, they can start the antibiotic empirically. It's really important that these patients understand that they're at risk for infection, even if it's a small risk.

Make sure that any communication breakdown doesn't originate at your end.

• ***Make sure referring doctors are on board with your management plans.*** High-quality postoperative care is time-consuming, and no one will work harder than you to salvage the bleb on a trabeculectomy that isn't performing. So if you have to leave postoperative care to another doctor, the other doctor may not expend the energy needed to get the patient to the argon laser and cut a stitch. That's especially true if it's a hard suture to see or remove.

For this reason, as much as possible, we do our own postoperative care for our surgical glaucoma patients that live in our area. When patients come from the far reaches of the state, however, we may have to work with a local doctor. In that situation we do our best to convince the doctor that this is really important.

Unfortunately, this can have mixed results. For example, suppose a patient lives 300 miles away. I do the surgery and then I send the patient back home with a letter saying something like this: "I recommend a slow taper of steroid over three to four months. In addition, there are three scleral flap sutures that should be cut as needed to augment filtration. I rarely cut sutures during the first week, but I would strongly prefer performing suture lysis to putting the patient back on medications. Please let me know if suture lysis is required." I even give the doctor my cell phone number to make it as easy as possible for him to contact me.

Unfortunately, what often happens is that despite laying all of this out clearly, the patient comes back six months later with elevated pressure, back on medications, and no sutures have been cut. Meanwhile, there's been no communication from the other doctor. It may be that the other doctor just didn't put the energy into trying to make this work; maybe he never even looked at the letter I sent. Then when the pressure rose he simply put the patient back on medications rather than doing the suture lysis or release.

This is very frustrating.

One thing that may help—depending on the patient—is explaining the situation to the patient. That way, when the local doctor suggests putting the patient back on medication, the patient might say, "Well, Dr. Samuelson said you might be able to open up the drain a little bit so I won't have to use drops again." Of course, not all patients will be able to understand and participate in that way, but some may be up to it.

Whatever happens, make sure that any communication breakdown doesn't originate at your end. If someone drops the ball, make sure it isn't you. REVIEW

Dr. Samuelson is a founding partner and attending surgeon at Minnesota Eye Consultants in Minneapolis and an adjunct associate professor of ophthalmology at Hennepin County Medical Center and the University of Minnesota. He is a consultant for Alcon, as well as several competing companies in the glaucoma surgical space.

Should RLE Surgeons Brace for Dislocations?

A look at the data, and surgeon experience, regarding factors that influence the long-term stability of IOLs in the capsular bag.

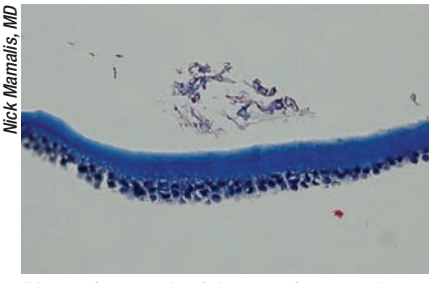
Walter Bethke, Editor in Chief

Pre-cataract presbyopes in their late 40s/early 50s who undergo clear lens extraction/IOL implantation often enjoy improved visual performance. Some surgeons wonder, however, if having IOLs in a large group of patients' eyes for 40 years will result in a wave of lens dislocations with time. In this article, the inaugural one for *Review*'s new section devoted to cataract and refractive surgery techniques, surgeons discuss the data on lens dislocations and what it might mean for long-term results.

Late Dislocations

Recent studies have looked at in-the-bag lens dislocations and their causative factors, and have mentioned that their incidence may be increasing.

Researchers in a joint U.S./German study in 2015, designed to analyze the IOL-capsular bag complexes in eyes in which the IOLs subluxated or dislocated, reported that they've received an increasing number of specimens related to in-the-bag subluxation or dislocation in recent years.[1] They refer to a previous study they performed in 2009 that looked at the possible causes of 86



Nick Mamalis, MD

Photomicrograph of the anterior capsule with exfoliative material seen anteriorly in a case of spontaneous IOL dislocation.

subluxations or dislocations, and note that just two of the specimens were submitted between 2000 and 2003 while 84 were submitted between 2006 and 2008.[2] A recent meta-analysis from Spain that looked at dislocation studies found that late in-the-bag subluxation or dislocation has been "reported with increasing frequency, leading to concerns of a pending large increase in IOL dislocations needing surgical intervention."[3] The researchers also cite a large, retrospective, population-based study that found the cumulative risk of IOL dislocation increases slowly with time, with a 1.7-percent risk after 25 years.[4] Though the rate of surgery related to late dislocations is low in the population-based study, the Spanish researchers say that the number of pseudophakes in the Western world is growing quickly as a result of improvements in phaco, longer lifespans and other factors, and that this might mean an increase in late dislocations.[3]

Given these studies, though, is this a problem surgeons should be worried about? Nick Mamalis, MD, director of the Ophthalmic Pathology Laboratory at the University of Utah's Moran Eye Center, isn't so sure. "The key question is: As we do cataract surgery on younger and younger patients, do we see them having more of a chance of spontaneous dislocation of the IOL within the capsular bag as the years go by?" he muses. "The good news is that we haven't seen signs of that, at least in the lenses that have spontaneously dislocated that are sent to our lab. In these lenses, the most common reason is pseudoexfoliation. When we did our first major lab study on that, we found that half of the specimens had dislocated secondary to exfoliation syndrome. But then, when we worked further with our German colleagues who sent us the IOLs within the capsular bags to analyze, even though a third of the patients had diagnosed

exfoliation prior to the dislocation we found that actually two-thirds of the cases had exfoliation."

The Capsulorhexis Connection

Another factor that some surgeons point to regarding a possible increased incidence of dislocations is the capsulorhexis. In a letter published in *Ophthalmology*, Los Altos, Calif., surgeon David Chang reported on two patients who had late dislocations, commenting, "The incidence of this delayed complication appears to have skyrocketed after universal adoption of the capsulorhexis technique."[5]

"I think one of the crucial issues in spontaneous IOL dislocation within the capsular bag is the use of a capsulorhexis," says Dr. Mamalis. "In the past, when we were doing can-opener capsulotomies and extracapsular surgeries, we just weren't seeing it happen. I think there's something to the idea that a good capsulorhexis, and an implant placed completely in the bag, can somehow, over many years, possibly lead to some constriction of the bag, some phymosis and some additional stretching of the zonules which could, in theory, put the patient at risk for a spontaneous dislocation. I say 'in theory' because we haven't seen any signs of this in the lab at this point."

George O. Waring IV, MD, medical director of the Medical University of South Carolina's Magill Vision Center and assistant professor of ophthalmology and director of refractive surgery at the MUSC's Storm Eye Institute, was one of the first surgeons to help surgeons and patients understand the term dysfunctional lens syndrome, and notes that nothing about the capsulorhexis has been definitively shown to cause dislocations down the line. He says neither femtosecond capsulotomies nor manual capsulorhexes will put a lot of stress on the zonules. "As far as capsular contraction goes, this would be an opportunity for lens epithelial cell eradication, and to date we don't have a way to do that," he says.

Lessons from Younger Eyes

Dr. Waring says ophthalmologists' experiences with the youngest of patients may help allay some fears of long-term dislocation.

"The best line of reasoning for this is pediatric cataract surgery," Dr. Waring says. "With refractive lens exchange, you're probably talking about someone who's already lived 50 years with his natural lens and is getting a lens replacement. But if you look at a cohort of infants or toddlers who are having IOLs implanted, they have their implants for more than 70 or 80 years, and we don't have any evidence that suggests that they'll have additional zonular issues because they have an implant. I think that we feel secure that this is still basically a non-concern."

Ultimately, Dr. Mamalis says long-term dislocations should be on the surgeon's radar, but maybe not a source of worry. "We haven't done cataract surgery with a capsulorhexis in people in their 40s and then followed them for 40 years because capsulorhexis hasn't been around for 40 years," he says. "We just don't know the answer regarding the risk of dislocation in these patients. I can say we haven't seen signs of it actually occurring, which is reassuring, but we just don't know. It's not a procedure that I would say we shouldn't be doing, but it's something we should keep an eye on." REVIEW

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Smaller, Brighter, Faster: The MacBook Pro 2016

A rich display and a speedy processor may be able to offer workstation capabilities in a portable package.

Kristine Brennan, Senior Associate Editor

Whether you want to run management software for your practice or visual acuity tests for your patients, a good notebook computer with brisk processing speed and standout graphics can allow you and your staff to get the job done without being shackled to an in-office workstation or testing system. In late October of last year, Apple unveiled the MacBook Pro 2016, the fourth generation of its MacBook line. This lightweight notebook is now available, and it comes in three versions: 13-in. without the new Touch Bar; 13-in. with Touch Bar; and the 15-in. MacBook Pro 2016 with standard Touch Bar. Any of the new MacBooks could accompany you wherever you go and provide a high-end work experience—but there are some limitations. Here's an initial look at the new laptop in case you were thinking of working it into your life and/or daily practice.

Under the Hood

Boasting its most thorough revamp since 2012, the MacBook Pro 2016 brings back Apple's proprietary Retina display, rendering lines seen on the monitor at 220 ppi unbroken to the eye when viewed at a normal distance. Available with a 13-inch or 15-inch monitor, both sizes are lighter than their predecessors: the 15-in. MacBook Pro 2016 weighs in at four pounds (1.83 kg), representing an eight-ounce slim down, while the 13-in. version is just over three pounds (1.37 kg), shedding just under half a pound compared to the previous version. The 15-in. and 13-in. MacBook Pros are both thinner with smaller footprints. The 15-in. version is 15.5 mm thick (14 percent thinner than the previous version) and 20 percent smaller overall, and its 13-in. counterpart is 14.9 mm thick (18 percent thinner than the previous version) and 23 percent smaller overall. This translates to considerable portability at either size, making the new MacBook Pro suitable for running software while floating from office to office, or for running visual acuity testing in non-office settings as needed.

The MacBook Pro's new profile doesn't come at the expense of its graphic display. The 13-in. notebook has a screen resolution of 2560 x 1600 pixels; the 15-in. model has 2,880 x 1,800. Apple claims that the DCI-P3 color space of the Macbook Pro is 25 percent broader than that of competitors with a conventional RGB color gamut. The graphics are also 67 percent brighter than before, according to Apple.

"The 2016 MacBook Pro's P3 color gamut helps it show a wider range of colors, with more realistic hues," says Susie Ochs, executive editor of *Macworld* magazine. "Oranges and deep greens are the most noticeable difference, but you might have to view the same images side-by-side with an RGB display to tell. The MacBook Pro is the first laptop to have a P3 display, which Apple previously introduced with the 4K and 5K Retina iMac line, and the screen is also much brighter." In terms of audio, the speakers are also louder and clearer than those on older MacBooks.

Apple also says that the new MacBook Pro's graphics are 130 percent faster than in prior MacBooks in the 15-in. laptop, and 103 percent faster in the 13-in. version. The disk

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speed is modestly faster than before in both—a consideration when it comes to copying files. "The processor speeds aren't a huge jump from the last model, but if you're upgrading from a Mac that's a couple years old or older, this should feel faster," says Ochs.

The Touch Bar

The most immediately obvious change in the MacBook Pro, though, comes standard on the 15-in. model and is optional on the 13-in. version: the Touch Bar. Apple's Touch Bar is a glass strip of organic light-emitting diode (OLED) display that replaces the row of function keys typically found at the top of the keyboard. Unlike dedicated keys, the Touch Bar's context-sensitive, illuminated icons change depending upon what the user is doing. For example, a user sending emails, texts or notes in Messages will find that the Touch Bar lights up with functions to support that—including emoji options. Users can also make one-touch online purchases using Apple Pay. The Touch Bar is customizable with some compatible applications, allowing users to add helpful commands and to eliminate others. The MacBook Pro's Touch ID sensor replaces the traditional typed login for added efficiency and security.

A Few Caveats

For all of its enhanced brightness, processing speed and other bells and whistles, however, a few changes to the latest crop of MacBooks may give some practitioners pause. The ultra-sleek notebooks no longer have SD card slots, and although Apple says that the new MacBooks have a battery life of about 10 hours, they no longer use MagSafe power adapters, the familiar magnetic adapters that break free from the port if enough tension is applied. Consequently, if someone or something snags a cable during charging, a broken MacBook Pro 2016 may result.

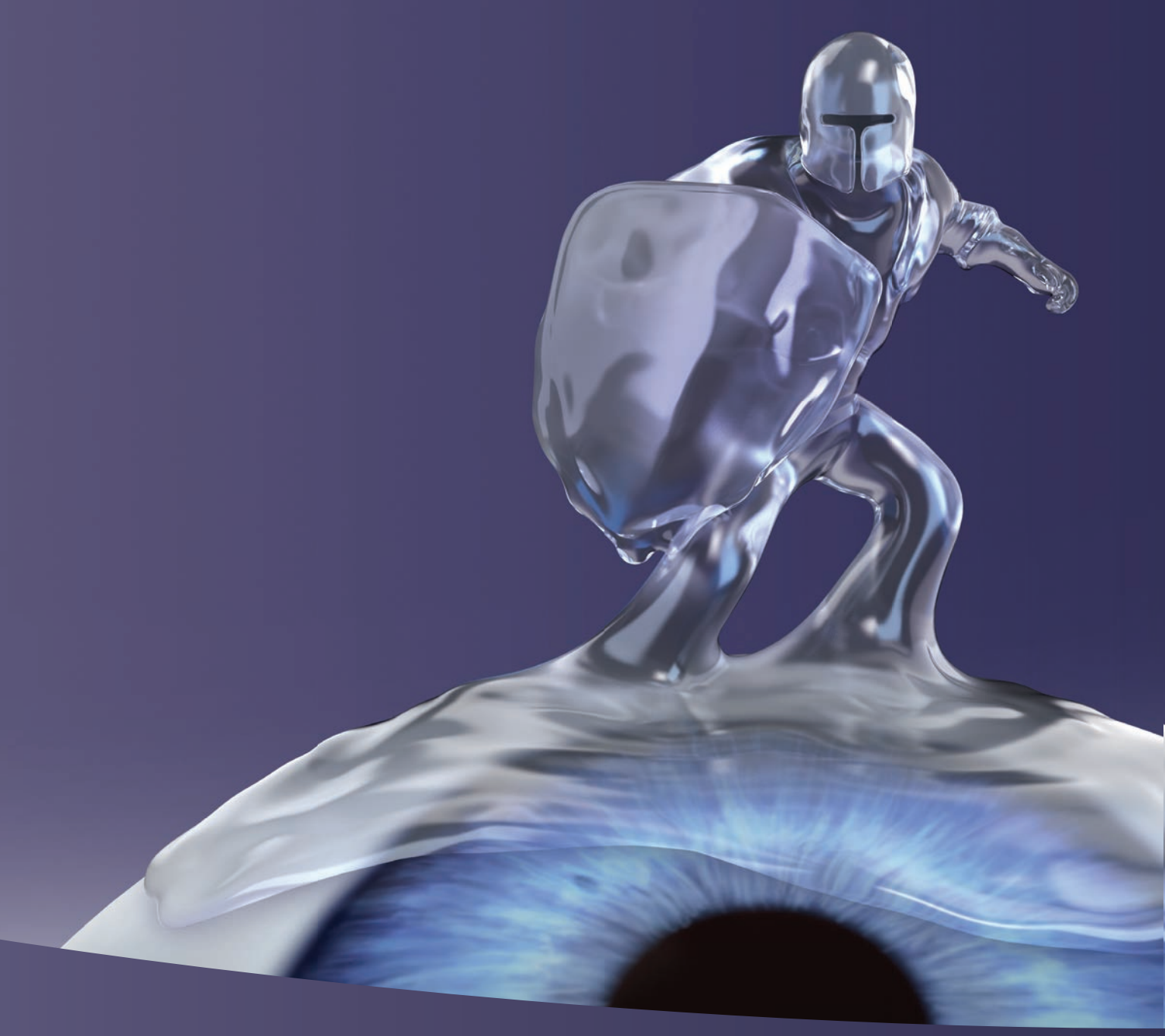
Apple

The Macbook Pro 2016 features a DCI-P3 color gamut in all three versions. The Touch Bar is available on two of them.

The new MacBook Pro doesn't have any standard USB ports, instead featuring Thunderbolt 3 USB-C ports (one on each side for the smaller model; two on each side for the larger one). Users who rely on secondary cameras, monitor screens or backup drives for their workflow will therefore have to purchase adapters. The Touch Bar itself may affect workflow, since it takes swiping along the Touch Bar and tapping the selected icon to do many things that formerly took just one tap of a dedicated key, such as adjusting brightness or speaker volume. Some users may miss having a permanent escape key, but the MacBook Pro 2016 should bring it up on the Touch Bar if it thinks an escape key is needed for the task at hand. Simply clicking the desktop screen will also restore the escape key to the Touch Bar, along with the primary function keys. The touchpads on all of the new MacBook Pros have doubled in size, and feature Apple's Force Touch haptics, which allow users to perform different functions with the touchpad by applying varying levels of pressure. However, this sensitivity, plus the increased real estate that the new touchpads take up, means that an errant brush of the wrist may open unwanted functions, at least until users adapt.

For doctors who want a work-worthy notebook with premium features, the MacBook Pro 2016 may be the prescription for a workstation-like experience in a lightweight package. As mentioned previously, however, power users who depend on secondary monitors and peripherals should be prepared to invest in Apple's proprietary adaptors.

"The biggest snag in integrating it into a practice could be its ports—the four [in the 15-inch model] Thunderbolt 3 ports support USB-C devices, but you'll need adapters to add USB Type A, Ethernet, HDMI or SD card ports as required," observes Ochs. REVIEW



Indications and Usage
BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

  It is recommended that BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular

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- Ensures complete coverage throughout the day with BID dosing[1]

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surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

- BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.
- The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

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.

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

NSAID=nonsteroidal anti-inflammatory drug.

References: 1. BromSite [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139. **4.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1. Accessed July 18, 2016. **5.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66.

SUN OPHTHALMICS

BromSite™ (bromfenac ophthalmic solution) 0.075% Brief Summary

INDICATIONS AND USAGE
BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of BromSite should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Use with Other Topical Ophthalmic Medications
BromSite should be administered at least 5 minutes after instillation of other topical medications.

Dosage Forms and Strengths
Topical ophthalmic solution: bromfenac 0.075%.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Slow or Delayed Healing
All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue
With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear
BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.

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

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS
Pregnancy

Risk Summary
There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations
Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of BromSite during late pregnancy should be avoided.

Data
Animal Data
Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m^2 basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m^2 basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 18 years have not been established.

Geriatric Use
There is no evidence that the efficacy or safety profiles for BromSite differ in patients 65 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m^2 basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m^2 basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m^2 basis).

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, advise patients to administer BromSite at least 5 minutes after instillation of other topical medications.

Concomitant Use of Contact Lenses
Advise patients not to wear contact lenses during administration of BromSite. The preservative in this product, benzalkonium chloride, may be absorbed by soft contact lenses.

Sterility of Dropper Tip/Product Use
Advise patients to replace the bottle cap after use and do not touch the dropper tip to any surface as this may contaminate the contents.

Advise patients to thoroughly wash hands prior to using BromSite.

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SUN OPHTHALMICS

In Search of the Perfect IOL Formula

Christopher Kent, Senior Editor

Experts offer advice on which formulas to use and how best to use them.

As every cataract surgeon knows, there are a number of formulas that can be used to decide what intraocular lens power should be implanted in a given eye. But how do you know which formula (or formulas) to use? Is one better than another? Can you use a single formula, or should you plug your numbers into several and compare the results? How much difference does it make to use a formula with seven variables instead of two? These are complex questions, and many surgeons disagree about the answers.

Here, to shed light on this topic, three surgeons with extensive experience developing and using these formulas share their thoughts.

Formula Evolution

As our understanding of the eye's anatomy has improved, the complexity of the predictive formulas for IOL power has increased. That's not the result of a change in our understanding of optics; it's because of refinement in our ability to predict where the IOL will sit inside the eye. "All the theoretical formulas use the same vergence formula to relate the cornea, the lens and the distances between them," says Jack T. Holladay, MD, MSEE, FACS, clinical professor of ophthalmology at Baylor College of Medicine in Houston and developer of the Holladay I and Holladay II formulas. "That vergence formula was first published by Stanilov Fyodorov back in 1975.[1] The only thing that's different [among the current theoretical formulas] is the prediction of the effective lens position. Prior to about 1970, everybody used about 4.5 mm for the axial length of every eye. Then Richard Binkhorst, MD, suggested that if the axial length is 10 percent longer than average, we should use a value 10 percent greater than 4.5 to calculate the ELP, and if the eye is 10 percent shorter, a value 10 percent smaller. He was the first person to individualize this.

"For many years, most of the formulas, including the Holladay I, SRK/T and Hoffer Q, just required inputting axial length and K-reading, because those were the measurements we had back then," he continues. "Then Thomas Olsen, MD, PhD, came out with a formula using four predictors: axial length; K-reading; anterior chamber depth; and lens thickness. In 1992 our team created the Holladay II formula, using seven variables to predict the effective lens position. Then Olsen and Barrett followed with new seven-variable formulas of their own. These formulas use axial length, K-reading, anterior chamber depth, lens

Should You Use Multiple Formulas?

Given the proliferation of calculation formulas with no clear winner in terms of accuracy, many surgeons believe it makes sense to plug their numbers into multiple formulas and compare and/or average the results. Douglas D. Koch, MD, professor of ophthalmology at Baylor College of Medicine in Houston, favors this approach. "I usually use the Holladay I with the Wang-Koch modification, the Barrett Universal II and the Hill-RBF," he says. "In short eyes, particularly those with a shallow anterior chamber, we also use the Olsen and Holladay II formulas. I look for consensus and may edge one way or the other, depending upon the accuracy of the measurements. If one of the three formulas doesn't agree with the others, I try to find a reason. Also, I may favor one formula based on certain features. If it's a long eye, for example, I may go a little bit more with the Holladay I—with the Wang-Koch modification—and the Barrett formula."

Uday Devgan, MD, FACS, FRCS, clinical professor of ophthalmology at the Jules Stein Eye Institute in Los Angeles, believes plugging your measurements into multiple formulas is unnecessary. "The Ladas Super Formula brings together the strengths of many formulas while avoiding their weaknesses," he says. "I tell surgeons, look at the outcomes of the last 50 or 100 cataracts you did. Now, calculate the powers for each case using the Ladas Super Formula at IOLcalc.com and see if the outcomes would have been better. The proof is in the pudding."

Jack T. Holladay, MD, FACS, clinical professor of ophthalmology at Baylor College of Medicine, is also skeptical that plugging your measurements into multiple formulas makes much sense. "Most surgeons who do that are using the older formulas," he says. "All that does is average formulas that produce less-reliable results. You're still not differentiating between a normal anterior segment and a small anterior segment, for example. It's a lot better to use a seven-variable predictor that takes more of the anatomy of the eye into account. It might make sense to average the three seven-variable formulas, but their recommendations aren't that far apart, so I'm not sure how much you'd gain."

Dr. Holladay is skeptical of the Ladas Super Formula for the same reason. "The Super Formula uses a combination of older formulas sorted for different kinds of eyes, but that's what the seven-variable predictors already do using a single formula," he says. "When you work with the older formulas you still haven't measured enough of the variables to really understand what makes the eye unique." Dr. Holladay also has reservations about simply basing the formula on a very large dataset. "It's certainly true that the size of the dataset makes a difference," he says. "However, I still believe it won't do you any good if you don't have the right details about the eye's anatomy plugged into the formula. A larger volume of cases can't compensate for missing information. Without that information you're not going to be accurate about which part of the pool the eye you're working with falls into."

—CK

thickness, corneal diameter, refraction and some, like the Holladay II, the age of the patient."

"IOL power calculation formulas have come a long way," agrees Uday Devgan, MD, FACS, FRCS, in private practice at Devgan Eye Surgery in Beverly Hills, chief of ophthalmology at the Olive View UCLA Medical Center and clinical professor of ophthalmology at the Jules Stein Eye Institute in Los Angeles. (Dr. Devgan helped to develop the Ladas Super Formula.) "For a long time people were using what are called the third-generation formulas—Hoffer Q, Holladay I and SRK/T. Those were the first to go beyond the most basic notions about how to calculate IOL power. Over time, surgeons reached a general consensus about how to use these formulas: The Holladay I formula produces the most accurate results with average eyes; the Hoffer Q works best with shorter eyes (hyperopic, small eyes with a short axial length); and the SRK/T formula produces the best results with longer eyes. So surgeons used whichever formula seemed most appropriate for the eye in question.

"Eventually, surgeons developed fourth-generation formulas which incorporate additional data," he says. "The Haigis formula requires the K-reading and the axial length, but also requires the anterior chamber depth. The Holladay II formula incorporates seven variables. Then people began suggesting fudge factors to refine the outcomes even further. Doug Koch and Li Wang from Baylor College of Medicine published a very good study about axial length adjustment in highly myopic eyes. They provided a factor [the Wang-Koch modification] to apply to your measurements if the eye is more than 25 or 26 mm long.

"By this point," he notes, "the formulas had become very convoluted. I literally had a flow chart on my desk: If this, then that. If that, then this. It became very cumbersome."

Trying to Simplify

Dr. Devgan says the newest formulas are trying to find ways to simplify the calculation process without giving up any accuracy. "Graham Barrett has created the Barrett Universal Formula, which is meant to work for all eyes," he says. "Hill-RBF refers to a radial basis function; it's a big-data/neural-net-based formula, incorporating data from thousands of eyes. It's not a specific equation; instead, it's a method of using existing data to predict results for your set of measurements.

"Finally, the Ladas Super Formula incorporates many existing formulas into a single equation that shifts your measurements into the right formula automatically," he explains. "If you're dealing with a short eye, the Super Formula uses the equations that get the best results with short eyes to generate a result. It also incorporates data from 100,000 surgeries and constantly improves its accuracy based on new

data that's coming in. The addition of crowd-sourced data lets you be pretty darn accurate. It can also give you an answer based on data from your own past results. But any of the latest formulas, including the Ladas Super Formula, the Barrett Universal II and the Hill-RBF, should give surgeons great results, as long as they're paying close attention to the details."

Is One Formula the Best?

This is a tricky question to answer, in part because some formulas seem to give better results in certain types of eyes (short vs. long eyes, for example), and in part because not much research has been done comparing formulas.

The development of each formula has been different as well. "Everyone who develops a formula says his is the best," notes Dr. Holladay. "It's not necessarily that people are biased; it's that formulas are developed based on a set of data, and the formula is refined until it produces the best outcomes—with that dataset. If you develop your formula using 300 cases, your formula is always going to be the best with that dataset because you've tweaked your formula until it produced the best results. Whether it will produce the best results with every other set of cases is a different question."

"There aren't many studies comparing recent formulas such as the Barrett Universal II and Hill-RBF," notes Douglas D. Koch, MD, professor of ophthalmology at Baylor College of Medicine in Houston. (Dr. Koch and Li Wang, MD, PhD, created the Wang-Koch modification.) "The best data I've seen was more than 90 percent of eyes within 0.5 D of predicted outcome for the Hill-RBF in normal eyes. I also still find the Holladay I to be an excellent formula, and I now also routinely use the Barrett Universal II. I've seen data that suggests that the Barrett Universal II formula does very well in long eyes, but perhaps not quite as well as the Holladay I formula combined with our Wang-Koch modification. In short eyes, we have some preliminary data that suggests that the Hill-RBF formula is a little better than some other formulas. It's also important to point out that both the Hill-RBF and Barrett are constantly being evaluated for ongoing improvement. Overall, they're all pretty close."

"The more you know about the anatomy of the eye and the patient, the better you'll be able to predict the effective lens position."
—Jack Holladay, MD

Dr. Devgan says he's had great success using the Ladas Super Formula that he helped to develop. "We're able to get 90-plus percent of eyes within half a diopter," he says. "The older, third-generation formulas usually only get about 70 percent within a half diopter. That's a big difference. In addition, I can now outsource the lens calculations to someone else in my practice. We just plug the numbers in and the calculation is done. Right now we have a Ladas Super Formula program that can be installed on your biometer that will automatically import the data to eliminate transcription errors. We're also working on adding character recognition technology to the Ladas Super Formula app we're developing, so you'll be able to use your phone to take a photo of the printout from the IOLMaster or LenStar and it will automatically pick up all of the data."

Dr. Devgan also appreciates being able to base the result on either crowd-sourced data or his own previously entered data. "I've entered data from a thousand eyes of my own," he notes. "I know that my results with myopic eyes tend to be pretty spot on, so I can just use my own previous results to determine what I should do. When I'm operating on an unusual eye where I don't have many previous data points to work with, I can use the data others have turned in when operating on similar eyes. I might see an eye like that once every five years, but with input from thousands of surgeons, the formula has plenty of data to work with."

Dr. Devgan points out that surgeons wanting to try the Ladas Super Formula can access it for free at IOLcalc.com. "An app with the formula is coming soon for both the iPhone and Android devices," he says. "The formula can also be installed on an instrument like the LenStar or IOLMaster."

Why Use Seven Variables?

"The reason it makes sense to use a formula with seven variables is that the more you know about the anatomy of the eye and the patient, the better you'll be able to predict the effective lens position," explains Dr. Holladay. "Here's a specific example involving the Holladay II formula. Our group was working with James Gills, MD, on a group of eyes that needed lenses between 40 and 60 D because the eyes were so short—from 15 to 20 mm long. The outcomes we achieved were mixed. Some we got right; others we missed by as much as 6 D.

"To try and figure out the reason for this, we went back and measured six anatomic characteristics of these eyes," he says. "We found that the white-to-white measurement—the corneal diameter—was the most helpful of the six measurements in terms of explaining the discrepancy. We discovered that these very small

eyes fell into two categories: Some short eyes had small anterior segments and small white-to-white measurements; but other short eyes had a normal anterior segment rather than a small one. The latter eyes also had corneal diameters of 11.8 or 12 mm.

"Most surgeons assume that short eyes have short anterior segments," he continues. "In fact, those two measurements are independent. We realized that there are two kinds of short eyes: those that are proportionally small, like a pygmy eye (nanopthalmos), and those that have a short posterior segment—axial hyperopia—but a normal anterior segment. The problem is, you can't tell which is which from the axial length and the K-reading; some short eyes had steep K's and some had flat K's. The white-to-white measurement was the only way to tell which type of short eye we were dealing with. And those with 12-mm corneas ended up with lenses sitting much deeper in the eye than those that had a small anterior segment."

Anterior Segment Size vs. Axial Length

Anterior Segment Size	Short	Normal	Long
Large	Megalocornea + axial hyperopia (0%)	Megalocornea (2%)	Large Eye Bupthalmos Megalocornea + axial myopia (10%)
Normal	axial hyperopia (80%)	normal (96%)	axial myopia (90%)
Small	Small eye Nanophthalmia (20%)	Microcornea (2%)	Microcornea + axial myopia (0%)

Axial Length

Surgeons have traditionally assumed that short eyes have shallow anterior segments and long eyes have deep anterior segments, but research by Jack Holladay, MD, MSEE, FACS and James Gills, MD, found that this isn't the case.

Dr. Holladay has created a chart that illustrates this point *[above]*. "You can divide eyes along two axes: the axial length and the size of the anterior segment," he says. "That leaves you with nine categories, ranging from long eyes with shallow anterior segments to short eyes with deep anterior segments. Most people have traditionally assumed that eyes fall into the boxes along the diagonal—that short eyes have shallow anterior segments and long eyes have deep anterior segments. But as our measurements found, that's only true of short eyes 20 percent of the time, and only true in long eyes 10 percent of the time. Eighty to 90 percent of the time, both types of eyes have a normal anterior segment depth. That's one of the mistakes surgeons make with the two-variable formulas; those formulas assume that short eyes have shallow anterior segments, which is only true 20 percent of the time. The seven-variable formulas correct for that mistake.

"Once we took this into account, all of a sudden we were no longer making those 6-D errors," he says. "We got the eyes that were proportionally small right, and the eyes that had big anterior segments but short posterior segments right as well. So having the extra measurements can make a big difference in many eyes. In fact, studies conducted by the lens manufacturers, as well as independent groups, have confirmed that the seven-variable formulas produce the most accurate results.[2-14] Of course, the lenses those formulas recommend may not be exactly the same because the datasets used to develop them were different. But when applied to new datasets, there's no statistically significant difference that would allow you to say that, overall, one formula is better than another."

If a seven-variable formula like the Holladay II is more accurate, does it still make sense to use the Wang-Koch modifier? "We've verified that the Holladay I version of the Wang-Koch formula works equally well for the Holladay II, so we use the Wang-Koch modification for all eyes 25.2 mm and longer," says Dr. Koch. (Dr. Holladay, incidentally, agrees that the Wang-Koch modification increases accuracy when dealing with long eyes. He believes the need for compensation results from optical biometers producing exaggerated measurements when the eyes being measured exceed 25 mm.)

When Dr. Holladay teaches classes in this subject, he offers his students two basic pieces of advice. "Number one," he says, "personalize your constant; otherwise there's no reason to worry about the formula because your result will be off anyway. Second, the seven-predictor formulas are the best, although there's no clear winner among them; each one produces a slightly different recommendation, and which is the best depends on your dataset. If you use a seven-predictor formula and personalize your constant, you'll get more than 90 percent of your cases within half a diopter."

Accurate Input Counts

Dr. Koch points out that almost all formulas are subject to two sources of uncertainty: the method the formula uses to calculate the ELP, and the accuracy of the measurements you're putting into the formula. "This is especially true of corneal measurements," he says. "I measure with two biometers and look at three sets of K-readings from different devices, but I still sometimes get postoperative refractive errors greater than half a diopter. In my Jackson Memorial lecture at the American Academy of Ophthalmology meeting this year, I gave an example

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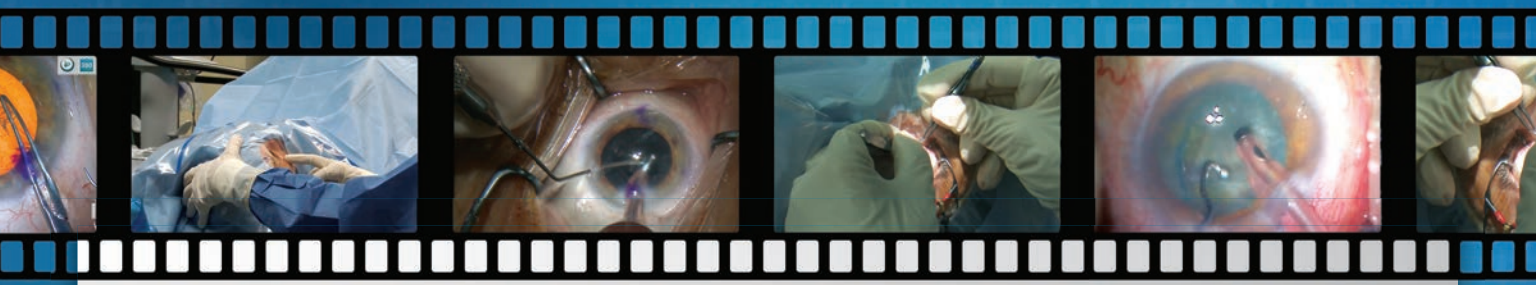

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Welcome to the second year of Mackool Online CME! With the generous support of several ophthalmic companies, I am honored to have our viewers join me in the operating room as I demonstrate the technology and techniques that I have found to be most valuable, and that I hope are helpful to many of my colleagues. We continue to edit the videos only to either change camera perspective or to reduce down time – allowing you to observe every step of the procedure.

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

Episode 13: "Correction of Negative Dysphotopsia by Optic Capture After Capsulorhexis Enlargement"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
This patient underwent cataract-implant surgery 3 weeks ago, has severe negative dysphotopsia and, fortuitously, a mild hyperopic refractive error. However, the preexisting capsulorhexis is too small to permit the optic to be captured. In this video, I demonstrate rhexis enlargement prior to successful capture of the lens optic.

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:

- Demonstrate capsulorhexis capture of the optic of an IOL.

Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for the Advancement of Human Behavior (IAHB) and Postgraduate Healthcare Education, LLC (PHE). IAHB is accredited by the ACCME to provide continuing medical education for physicians.

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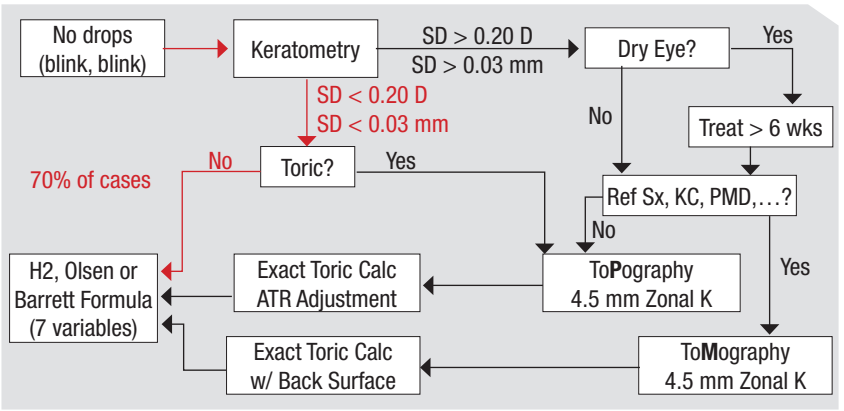
of this. The K-reading I measured for one patient was 44.1, and the patient ended up myopic postoperatively. I remeasured the patient two weeks later and got a reading of 44.6, which was enough of a difference to account for the error. Even with careful measuring and our advanced technology, this can still happen. You just have to do your best and make sure your patients understand that the outcome won't always be what you expect it to be."

Dr. Koch says both the LenStar and IOLMaster produce good results when used correctly. "I use both," he says. "I do prefer the IOLMaster 700 to the IOLMaster 500; I find the corneal power measurements are superior, and the 700 has greater accuracy when measuring anterior chamber depth. The IOLMaster 700 is also the most robust biometer for measuring axial length in eyes with dense cataracts. One limitation of the 700, however, is that while it includes the Holladay II formula, it doesn't include the Barrett or Hill-RBF formulas. The LenStar offers all three, along with a version of the Olsen formula that's not quite as sophisticated as the one you can purchase directly from Dr. Olsen. I presume the IOLMaster will expand their formula options as time goes by. In the meantime, if you have the IOLMaster and want to use all three formulas, you can use the Barrett and Hill-RBF formulas online at the ASCRS website.

"Whichever instrument you use, it's important to look at the quality and consistency of the data," he continues. "With the IOLMaster, you can look at the images that are reflected off the cornea from the instrument's 18 LED lights; you may see that some of the reflections are smudgy instead of sharp. That tells you that the reading may not be as accurate as it should be. With the LenStar you can look at the standard deviations of its six corneal power measurements of the flat and steep meridians, as well as the astigmatic axis. With any measurement for IOL calculations, you need to validate the quality of the measurement."

Dr. Holladay's Corneal Power Decision Tree



Jack Holladay, MD, MSEE, FACS, recommends using this decision tree to determine the power of the lens you should implant to get as close as possible to your desired outcome. The majority of eyes should follow the decision path marked in red.

Dr. Koch says it's also important to validate topography measurements, especially in terms of astigmatism. "It's important to use a topographer that gives you information about the quality of the corneal surface," he says. "I use the Gallilei topographer, which has both placido disc and Scheimpflug technology. It tells me a number of important things. First, it tells me if the mires are distorted, which means that the corneal surface is irregular and that I need to fix that before proceeding with surgery. Second, it gives me the magnitude and meridian of any astigmatism for comparing to the LenStar and IOLMaster measurements. Third, it tells me if there are any abnormalities in corneal curvature, any irregular astigmatism or other factors that might influence my IOL selection or my ability to safely use excimer laser surgery to treat the patient after I put in a premium IOL, should I need to do a postoperative adjustment."

Holladay I or Holladay II?

Some surgeons report that they've gotten better results using the Holladay I formula than the Holladay II seven-variable formula. Dr. Holladay says that in his experience, this is because surgeons often input the refraction they measure at the preoperative visit. "That refraction has been altered by the cataract," he explains. "The refraction helps the formula determine the size of the eye, but only if it's the adult refraction before the cataract formed. Someone who was plano at age 21 might appear to be -4 D when measured right before cataract surgery. A person who really was -4 D as an adult before developing a cataract will have a thicker and more powerful crystalline lens than an average person. In those people, the lens you implant is going to end up in a different position than it will in an eye that was emmetropic before the cataract formed. If the eye you measure as -4 D right before the surgery was plano before the cataract, putting -4 D into the formula will throw your result off.

"Also, don't use an average for something like lens thickness if you're not able to measure it," he continues. "If the eye isn't average you'll get a worse answer than if you just leave the number blank. As a rule, never put in values that you haven't measured."

Dr. Holladay admits that getting the patient's previous refraction is more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work. "That's one reason many surgeons don't do it," he says. "If you're seeing the patient for the first time, you have to ask the patient for help. He may still have the glasses he wore before he had LASIK. Or, you can ask questions like: 'Were you able to get your driver's license without wearing glasses?' If the patient says yes, you know the patient was probably emmetropic. Many people can tell you how far away things had to be in order to see them clearly when they were in their 20s. Any of these things can give you a good approximation of the precataract refraction. Just don't use the manifest refraction measured on the visit before the cataract surgery."

Formula vs. Intraop Refraction

Given that calculation formulas keep improving, some surgeons believe that intraoperative aphakic measurement—where the surgeon uses a tool like the ORA or HOLOS to take a refraction while the patient is on the operating table—may eventually become unnecessary. "I think better formulas and preoperative measurements will eventually reduce the indications for intraoperative aberrometry, but we're not there yet," says Dr. Koch. "That's particularly true for astigmatism, and I still use this technology routinely for post-LASIK eyes. But I'm already using it a bit less than I used to."

Dr. Holladay believes that no matter how good lens power formulas become, tools like intraoperative aberrometry will still be useful because of the accuracy limits of preoperative measurements. "The limit of our accuracy in lens calculation is the sum of the variability of all of the measurements we have to take," he explains. "There will always be variability in the axial length measurement, and certainly in the K-reading, where we use a keratometer to measure the front radius of the cornea, assume that the back radius is 82 percent of that, assume an index of refraction and then calculate the power of the cornea.

"In contrast," he continues, "intraoperative refraction simply uses the cornea as a lens to measure the aphakic refraction. That eliminates the variability of all of those calculations and assumptions, particularly for people who have had refractive surgery or have an irregular cornea." (Dr. Holladay notes that in post-refractive surgery cases, the posterior surface radius is no longer 82 percent of the front surface radius, so measuring the back surface using tomography will increase the accuracy of your prediction.)

"We've spent 50 years doing intraocular lens calculations and we're reaching a plateau at about 90 percent of eyes within half a diopter, in terms of accuracy," he points out. "The limit isn't the formula; the limit is the precision of the measurements that we put into the formula. If you look at it from an engineering perspective, the error of the answer is the sum of the squares of the error of each variable that goes into the formula. Our precision limit for the cornea is about 0.25 D; the error for axial length is about 0.1 mm; and the anterior chamber depth and the effective lens position is down to 0.2 or 0.3 mm. Those error limits keep us at about 90 percent of patients within half a diopter of the target outcome."

Dr. Holladay acknowledges that the accuracy of these measurements may still improve. "That remains to be seen, however," he says.

Dr. Devgan sees another possibility: incorporating an advanced formula into the intraoperative aberrometer. "Intraoperative aberrometry is more complicated than just the auto-refraction done on the table," he explains. "All formulas calculate two things: the vergence calculation and the effective lens position. The aberrometers tell us the vergence calculation, but they still have to calculate the ELP, and that makes a huge difference in the outcome. That's why the ORA requires you to input the K-reading, axial length and other biometric data before even starting the cataract surgery. So incorporating an advanced formula like the Ladas Super Formula into the intraoperative aberrometers should result in increased accuracy. It might be possible to get 99 percent of eyes within half a diopter." REVIEW

Dr. Holladay is a consultant for AMO, NIDEK, Oculus, Acufocus, Allergan, Zeiss and Wavetec. Dr. Devgan is a principal in Advanced Euclidean Solutions which owns the Ladas Super Formula and the IOLcalc.com website. Dr. Koch consults for Alcon, AMO and Holos and has previously consulted for Carl Zeiss Meditec.

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Calculating for Success: IOLs in Difficult Eyes

Kristine Brennan, Senior Associate Editor

Careful biometry and corneal health are as important as choice of formula.

Dr. Harold Ridley (1906-2001), who implanted the first intraocular lens in 1949, lived to see cataract surgery evolve into a true refractive procedure, undergoing IOL implantations himself in 1989 and 1990.[1] Today, outcomes within half a diopter or less of target are attainable in most normal eyes, but some cases continue to present challenges. This article provides insights from seasoned cataract surgeons about how to maximize your outcomes and includes brief discussions of specific types of challenging eyes.

Preop Workup is Critical

"I can have a long eye, a short eye or a post-LASIK eye, but the most important thing I do is give them all the same thorough preoperative workup," emphasizes P. Dee Stephenson, MD, FACS, president of the American College of Eye Surgeons, associate professor at University of South Florida College of Medicine in Tampa and CEO/CFO of Stephenson Eye Associates. "I use the IOLMaster 700, the Cassini and the iTrace on every patient. I also do an OCT of the macula to make sure there is no pathology."

Samir Sayegh, MD, PhD, FACS, of the Eye Center in Champaign, Ill., also considers a meticulous workup fundamental to a good refractive outcome. "We have a routine that applies to all eyes identified as being particularly exceptional," he says. "We do a lot of repeat testing. We do partial coherence interferometry using the IOLMaster for axial length, and we do ultrasound. We do both every time, for every patient. For the measurement of the K value, we use at least three methods. Another thing we do is OCT of the retina for all patients. We also do pachymetry on all patients."

Dr. Sayegh says these measures help to reveal any pathology ahead of time. "Everybody having cataract surgery will get OCT, and they will get evaluation of the thickness of the cornea, so that if there is underlying Fuchs' or anything that would be an issue at the time of surgery, we can take extra care with the eye. If there's anything that would show up later, in the postop results, we also want to know ahead of time."

"Anybody that comes into our office for an exam gets an aberrometry scan," says Brock K. Bakewell, MD, FACS, partner at Fishkind, Bakewell & Maltzman Eye Care in Tucson, Ariz., and adjunct associate professor of ophthalmology at the University of Utah. "We do an OPD using the Nidek system for aberrometry. I can look at that and usually tell if they've

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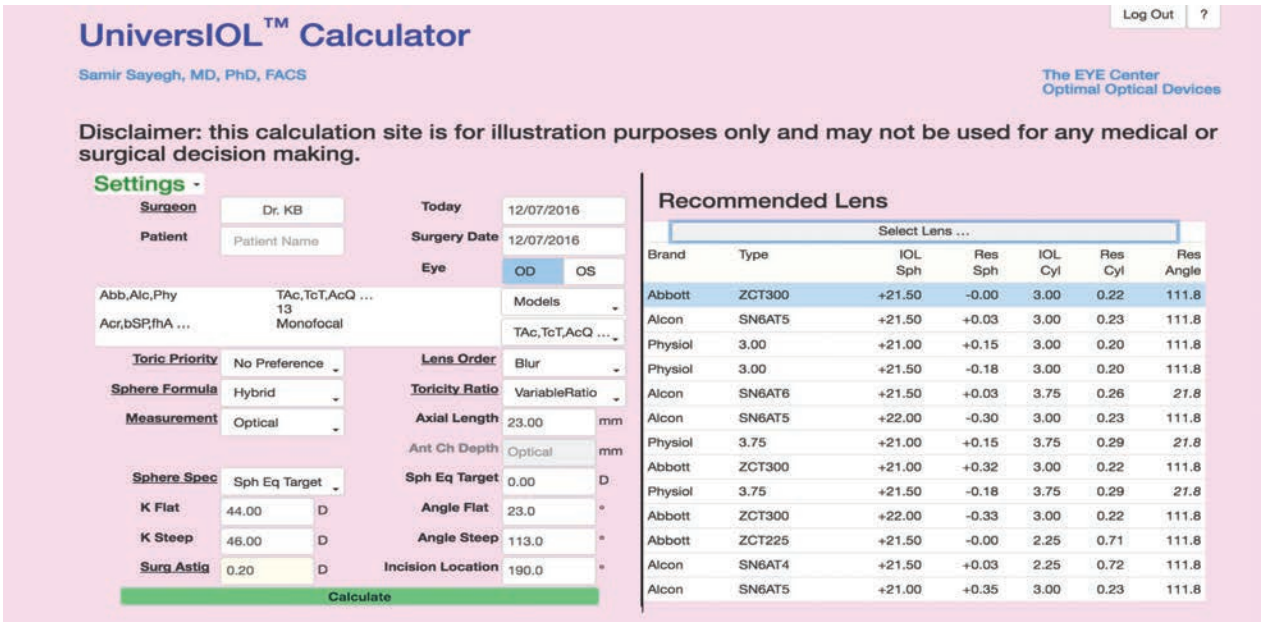

Samir Sayegh, MD, PhD, FACS

The UniversIOL Calculator's database includes a vast array of lenses. It also allows surgeons to enter spherical and toric data simultaneously and features multiple computation modes, including the Hybrid function, which runs multiple formulas and selects the best one.

had myopic or hyperopic LASIK just from looking at the aberrometer. You know how much spherical aberration patients have, and that dictates what lens you're going to put in the eye if you're going to try and balance that for the best optical outcome.

"The aberrometry is great, but you obviously also need a good examination at the slit lamp," continues Dr. Bakewell, who adds that he's had some patients forget to tell him about refractive surgery performed 15 or 20 years ago.

Stabilize the Ocular Surface

"Anybody who's doing cataract surgery needs to be aware of corneal surface disease," states Dr. Bakewell. "Dry eye can make your biometry measurements very inaccurate. If you get a lot of variability in your measurements, you should put your patients on drops and tune up the corneal surface before you take their final measurements prior to cataract surgery." He adds that map-dot-fingerprint surface dystrophy (anterior basement membrane corneal dystrophy) and Salzmann's nodules are two findings that must be addressed before doing final biometry. "If Salzmann's nodules affect the central cornea at all, they should be scraped two to three months prior to doing your measurements for cataract surgery," he says.

Dr. Sayegh adds, "Once you have a very good assessment of the state of the cornea with regard to astigmatism and any dryness, and you treat and stabilize it, then there's no reason to measure differently than with other eyes. Make sure that you have a stable K for a consistent reading."

Use Modern, Tested Formulas

Repeated measurements of a stable eye facilitate good IOL power calculations. So does the use of modern, yet tested formulas. "I look at all of the data I've collected and run calculations using multiple formulas," says Dr. Stephenson of her next step after workup. She has a repertoire of formulas that she uses consistently. "Right now, I use SRK/T, Barrett, Koch and Haigis," she says, adding that she notes she's been using more Barrett and less SRK/T and Haigis lately.

"The third- and fourth-generation formulas are the ones we should be using now," says Dr. Bakewell. "We used to run Holladay 1 and Holladay 2. Now our standards are pretty much the Barrett, the Olsen, and Warren Hill's new formula, the radial basis function (RBF)." He says that he runs this trio of formulas on every patient. "If you're trying to hit zero correction, using those formulas is going to get you within about half a diopter, plus or minus, of your target about 90 percent of the time," Dr. Bakewell estimates.

Dr. Sayegh and colleagues have developed the web-based UniversIOL Calculator (2020eyecenter.com/iol-calculator/) to help make searching for the single best formula for a given eye a thing of the past. "Everybody and their brother or sister has a formula," he quips. "But there are some that have stood the test of time. Some prove very effective, very consistently over large groups of eyes." Dr. Sayegh singles out the Haigis-L formula as one such example. His calculator incorporates third- and fourth-generation formulas and allows the surgeon to enter spherical data and toric data at the same time without switching from one calculator to another. It also contains ranked data for every IOL manufactured worldwide.

The UniversIOL Calculator will guide the selection of correctly powered IOLs for any lens model, but the surgeon can override its

recommendations. Users can also run one or multiple formulas simultaneously. "My calculator has a function called Hybrid, were it calculates all of them and it selects the one that is the best for that particular eye," Dr. Sayegh explains.

He adds that the Hybrid function is important because formulas may demonstrate instability when applied to certain difficult eyes. "Certain combinations of Ks and axial lengths in the SRK/T, for example, are unstable and will not give you a result that you should rely on," he explains. "So if the eye we are looking at is in that region, we exclude the SRK/T from being calculated. You can override the system and say you want to use the SRK/T anyway, but our Hybrid algorithm always chooses one formula that's consistent with all the published literature and is established to be the best in that parameter set."

Dr. Sayegh reports encouraging refractive outcomes. "People at -15 D, -16 D come very comfortably within ±0.5 D of target," he says. "Very often we get within ±0.25 D. The results are really very good. "

Post-refractive Surgery Eyes

Patients with prior refractive procedures may be expecting the same dramatic visual improvement after cataract surgery with IOL implantation that they enjoyed after LASIK, PRK or RK. "Prior refractive surgery patients have very high expectations," says Dr. Bakewell. "You always have to tell them that even with all the formulas we run, everything is a best guesstimate, and they still might come out a diopter wrong. If they do, I tell them I won't make them live with it. I'll offer them the option of exchanging the lens, for example."

Dr. Stephenson finds both the ASCRS calculator and the IOLMaster helpful in these eyes. "Optimizations for different post-refractive eyes are done for you using the IOLMaster after you plug in the data you have," she notes.

"Hopefully, anybody who has had RK has already had their cataract out," says Dr. Sayegh, adding that he hopes the procedure is now "a historical aberration that we don't have to encounter often." Faced with such an eye, Dr. Sayegh says he would refract it with a contact lens and then target for slight myopia. "If you implant something and they're still -3 D or -2 D and they don't like it, you wouldn't want to mess with their cornea. What you can do is implant a piggyback IOL. I think we'll get a few more of them in the United States in the next few years."

"We have an Orbscan for topography, and we do total axial power measurements on anybody who's had myopic PRK or LASIK or RK," says Dr. Bakewell. "Averaging the four central keratometry readings from the total axial power measurements gives an average K that we run in the Barrett formula. Since this average K is usually slightly flatter than the true K readings, one must choose an IOL power that shoots slightly on the hyperopic side, approximately 0.25 to 0.5 diopters. The ASCRS calculator for post-refractive surgery is also one of the best things to use, but still requires some interpolation due to the range of suggested IOL powers."

That is thought to be in part because myopic and hyperopic ablation procedures flatten or steepen the cornea, respectively, throwing off assumptions about corneal power in IOL formulas developed for surgically virgin eyes. Also, after myopic LASIK, IOL formulas relying on the relationship between anterior chamber depth and the steepness of the cornea to estimate the effective lens position can erroneously predict an artificially shallow lens position, leading surgeons to select an underpowered IOL, which plays a role in hyperopic surprise. After hyperopic LASIK, the surgically steepened cornea can lead to the opposite error: artificially deeper effective lens placement estimate and an overpowered IOL selection, a causative factor in myopic outcomes.[2]

"If they've had myopic LASIK, I'd rather leave patients slightly myopic versus hyperopic. Patients hate hyperopia. The other thing is that it's easier to correct myopia with PRK than hyperopia," says Dr. Bakewell.

Of prior hyperopic LASIK patients, he says, "Their Ks are a tiny bit steeper. They're read by the Lenstar or IOLMaster as a little bit flatter than they really are. For a patient with previous hyperopic LASIK, you're going to pick a lens that suggests a slight hyperopic result."

If you do end up with a small refractive surprise and an unhappy patient, resist intervening too soon, says Dr. Bakewell. "If you do a surgery and it comes out just 0.5 D or 0.75 D on the farsighted side, I would let the lens reside in the eye for approximately three months, because the refraction can change in the right direction. I recently had a patient who was hyperopic after myopic LASIK. She was +0.75 D after her cataract and IOL surgery. This lady was very unhappy, and wanted me to do something right away. I said, 'No. We need to wait,' and she ended up being -0.5 D three months later. So you don't want to be too quick to do a PRK or an IOL exchange. You really want to wait those three months for the lens to settle in and see if it changes position in the capsular bag with healing."

Short Axial Length

In eyes with short axial length the biggest challenge to a good refractive outcome is that the actual implant position may be more anterior in the eye than the estimated effective lens position indicates, causing calculation of an overpowered lens and a myopic surprise.

Dr. Sayegh believes that Hoffer Q

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is a good choice for IOL calculation in short eyes, based on consistent evidence in the literature. "There's not one, but dozens of papers, and each of those papers has 100, 200 or maybe thousands of eyes, so there's some consistency there, where you know that this has been tested again and again."

Dr. Bakewell says he tends to gravitate towards the Olsen formula for short axial lengths. "I used to use the Hoffer formula, but that's somewhat outdated. Holladay 2 is not bad, but I think the Olsen is probably best for short eyes."

Long Axial Length

IOL calculations in eyes with long axial length can lead to selection of an underpowered lens and hyperopic outcomes for multiple reasons: difficulty in obtaining an accurate measure of the axial length; an increase in the prediction error in formulae as axial length increases; inaccurate ELP; and IOL constants not suited to the long eye.[3] "If the eye is really long," says Dr. Bakewell, "I won't pick a lens that is projected to give me a zero result. I'm going to shoot for a lens that's got maybe -0.5 D, -0.75 D or even -1 D. I'd rather patients come out a tiny bit myopic than move them into farsightedness."

Dr. Sayegh considers the Wang-Koch modification optimal for long eyes. "If you have very long eyes, you can use the Holladay 1 or the SRK/T, for example, but for each of these formulas, they suggest you make a different corrective modification: You use not the true axial length, but the modified axial length, and they give you a formula to modify it." There are discrete Wang-Koch modifications to find the optimized axial length using the Haigis and Hoffer Q formulas, as well. Surgeons can currently enter Wang-Koch modifications directly into the UniversIOL calculator, but Dr. Sayegh is considering adding a mini-calculator to the Hybrid feature that would figure out the Wang-Koch modification using the true axial length, and then feed the converted AL into the final IOL calculations.

Staphyloma

Staphylomatous eyes make measuring the AL challenging. "The staphyloma throws you off as to where to fovea is," says Dr. Sayegh. "Your main problem is not which formula to use: The main problem is getting the correct axial length. We use partial coherence interferometry; we use ultrasound, doing multiple measurements with different devices, and we do a B scan. That will give you not just the length, but also the whole shape of the back of the eye. How the signal is bouncing can help you identify where the staphyloma is and get you a much more reliable reading. You want the distance between the cornea and the fovea. You also do OCT. With all of that information you determine what the true axial length is. You don't have to use any magic formula for staphyloma."

Dr. Bakewell emphasizes that being even a tiny bit lateral or nasal to the center of the staphyloma while trying to measure to the fovea can result in big refractive errors. "Being off one millimeter in the axial length translates to being off three diopters in lens implant power," he emphasizes. He runs the Barrett, Olsen, and Hill formulas for these eyes using an AL measurement to the fovea, and he fudges towards myopia. "Your formulas sometimes underestimate the power of the lens to put into these folks," he says. "Even if I'm trying to achieve plano, I'm shooting for -0.75 D or a -1 D, because frequently you're off a little bit in that direction."

Keratoconus and PK

Dr. Bakewell generally doesn't target plano in keratoconic eyes. "If the patient is a successful contact lens wearer with gas-permeable lenses, and is planning on wearing contacts after cataract surgery, I usually shoot to leave those patients on the myopic side, maybe -2.5 D to -3 D. That lets them see well enough to put their contacts in. If their keratoconus is significant, they are always going to need a contact in order to see their best. There's no reason to shoot for plano."

If the keratoconus is severe enough, and the cataract is not too debilitating, Dr. Bakewell will do a corneal transplant procedure first, then wait approximately nine months to a year for most of the sutures to be out before doing cataract surgery. "In terms of calculations you just use your regular formulas, but many times they have very irregular astigmatism, so they're difficult eyes," he says. "In terms of cataract surgery, keratoconics have very steep corneas, but if you do a corneal transplant, you're replacing their steep cornea with a flatter one. If you're taking power away from their eye, then the lens implant is going to have to be stronger, assuming you've already flattened their cornea. If you're doing cataract surgery prior to a corneal transplant, then you'll have to put a steeper-powered lens in than what your measurements call for, because your keratometry measurements might be four, six or eight diopters flatter after corneal transplantation. It's better to do the corneal transplant first if patients really need it. Your measurements are going to be much more accurate."

Dr. Sayegh does not believe that there is an all-purpose IOL formula for keratoconic/PK eyes, either. "What matters is an effective reading of the K. The problem is that their Ks are essentially variable. You have to stabilize the surface of the cornea and then bring them back for measurements," he says. "Post corneal transplant, you want to know what the potential vision was at the time of the corneal transplant, before they developed the cataract. Sometimes, the distortion at the level of the cornea is what really limits their

vision, not the cataract. These patients can do well with toric IOLs."

Dense Cataracts

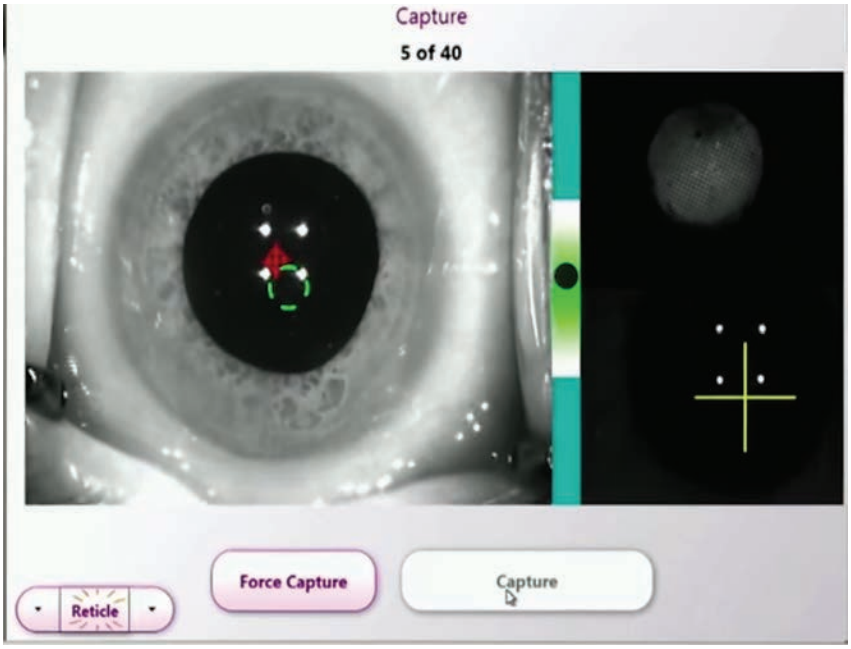
Dr. Sayegh reports that he sees a sizeable subset of patients with dense cataracts both in the United States and abroad because of their difficulties accessing health care at earlier stages. "For the advanced cataract, even with the new IOLMaster and some of the new partial coherence interferometry systems that penetrate more dense cataracts, you sometimes have to go to ultrasound," he says. "Ultrasound does it every time: It always gets results—not always as reproducible, but the differences are minimal—especially for patients who come to you with very poor vision in the first place."

Dr. Stephenson says the IOLMaster 700 makes good axial length measurements feasible in most advanced cataract cases. She also suggests measuring an unaffected fellow eye to help zero in on axial length, provided that eye has a stable refraction.

Intraoperative Aberrometry

For patients with dense cataracts—or any cataract patients—intraoperative aberrometry can help surgeons corroborate or fine-tune IOL power choices in challenging eyes. Research comparing Optiwave Refractive Analysis (ORA) with three preop methods of IOL calculation (surgeon's best choice; the Haigis- L, and the Shammas) in 246 eyes of 215 patients with a history of myopic LASIK or PRK demonstrated that eyes refracted intraoperatively with ORA had the lowest median absolute error at 0.35 D, and 94 percent of the ORA eyes were within ±1 D of the device's predicted outcome.[4]

Tal Raviv, MD, FACS, associate clinical professor of ophthalmology at New York Eye & Ear Infirmary of Mount Sinai, and founder and medical director of the Eye Center of New York, describes



Cynthia Matossian, MD, FACS

Intraoperative aberrometry can confirm or refine IOL power estimates.

intraoperative aberrometry as "invaluable for tough biometry cases such as very long axial length, mild to moderate keratoconus, and post-refractive eyes.

"In 2016 we have some very good 'no-history' IOL calculation methods available on the ASCRS calculator," Dr. Raviv continues. "However, using ORA has been shown to be more accurate in some studies. Furthermore, it is not uncommon for post-LASIK eyes to require a toric IOL, and no preoperative measurement can perfectly measure the true anterior and posterior astigmatism of these eyes. ORA allows the surgeon to neutralize the refractive astigmatism with high accuracy." He adds that surgical approach and sedation level are important considerations with ORA, since the device incorporates patient fixation into measurements. "During the Verifeye aphakic reading," he explains, "one can see the cylinder measurements jump significantly with very slight movements of the eye." Patient participation will yield more accurate results.

Dr. Stephenson goes in with her preop calculations prepared, but will move to what ORA recommends in the OR if there is a discrepancy. "The ORA can reference some 550,000 cases, and I'll err on the side of what it tells me intraoperatively," she says.

As IOL implantation inches closer to the long-term goal of emmetropia, surgeons implant challenging eyes with a more immediate goal: patient satisfaction and well-being. "You can plan all you want," says Dr. Stephenson, "but sometimes there are surprises, and you have to look at the gestalt of the situation and make a decision that you think will be best for the patient." REVIEW

Dr. Stephenson is a member of the speakers' bureau for Cassini and ORA/Alcon. Dr. Sayegh reports no financial disclosures. Dr. Bakewell is a consultant for AMO. Dr. Raviv is a consultant for AMO.

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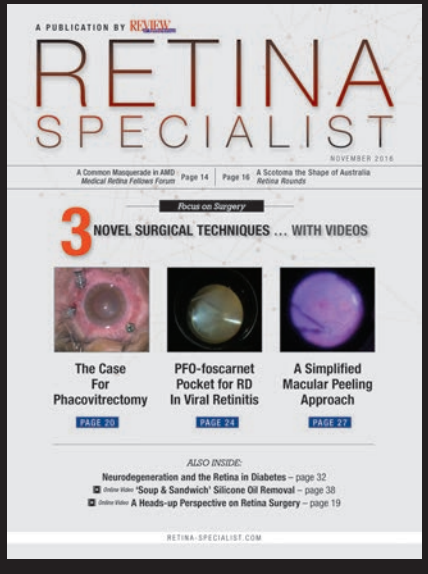

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Minimizing Your IOL Chair Time

Jeffrey S. Eisenberg, Contributing Editor

Ways to educate patients about their myriad options—and still have time left over to operate.

In 2010, an estimated 24.4 million individuals had cataracts, according to the National Eye Institute—and the number is expected to rise to some 38.7 million by 2030. Market Scope expects intraocular lens procedures to climb from roughly 24.4 million globally in 2015 to nearly 30 million in 2020 at a compounded annual rate of 3.6 percent. And, according to the ASCRS 2016 Clinical Survey, the average annual cataract volume continues to rise and now stands at 512 a year per surgeon.

And that's not counting IOL procedures other than cataract. "We're probably going to see more interest in presbyopic lens exchange because surgeons are getting more comfortable with newer technology and its availability," says R. Bruce Wallace III, of Alexandria, La.

Just as the number of cataract patients has risen, so too have the IOL options you can offer these patients. "One of our primary responsibilities as eye surgeons today is to help guide patients through a dizzying array of new technology," says Michael Colvard, MD, of Encino, Calif. "Our goal should be to help patients select the specific technology that best meets their needs and expectations, and you can't do this by simply giving patients a mind-boggling laundry list of options."

But, how do you accomplish this and still have enough time left over to actually perform the surgery? Here are some suggestions.

In the Mail

You don't need to wait until the patient is in the exam lane—or even in the office—to begin the education process. You can send the patient and family members introductory letters and brochures that provide information about your practice and introduce cataract surgery and IOLs to the patient ahead of time. Don't forget to include some information on your practice's website as well.

"This information gives the patient and his family the chance to begin understanding what will occur during his cataract evaluation and what will be discussed when they come to the office," says James Loden, MD, of Nashville, Tenn.

Another item to send patients in advance: a lifestyle survey such as the Dell questionnaire (developed by Austin, Texas, surgeon Steven Dell in 2004). The questionnaire should ask about the patient's preference for achieving distance or near vision without glasses, what activities the patient engages in and for which he would be willing to wear glasses, whether issues

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such as glare would bother him, and even how the patient sees his or her own personality.

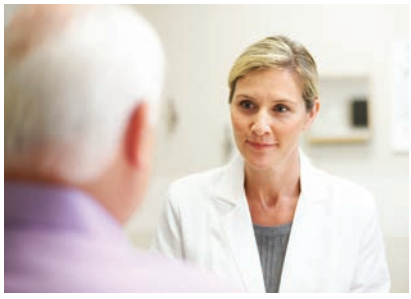
"By the time I see patients, they've given some thought as to their desire for spectacle independence," says Daniel H. Chang, MD, of Bakersfield, Calif. In his questionnaire, Dr. Chang also asks patients if they would be willing to pay extra if they could potentially avoid needing glasses. (Medicare requires that you inform patients prior to surgery that Medicare will not pay for services specific to the insertion, adjustment and other subsequent treatments related to premium IOLs and vision-correcting technology.) This gets the discussion started.

Once the patient arrives at the office, you can continue the education process right in your waiting room or further into the visit as patients dilate. For example, software and videos are available from such companies as Rendia (formerly Eyemaginations) and Patient Education Concepts—some of which let you select only those options suitable for the patient.

In the Office

Once the patient is in the exam lane, if you've had him fill out the Dell questionnaire or something similar, you'll know whether he wants distance or near vision without glasses, whether the patient is willing to tolerate a certain amount of glare, and what the patient's vocations and avocations are.

"I ask the patient: 'In a best-case scenario, what are you hoping to achieve with cataract surgery?' " Dr. Colvard says. "The answer almost always is, 'I want to see better.' So then I ask, 'How important is it to you to reduce your dependency on glasses?' This introduces the concept that there are possibilities beyond just better vision with glasses. And it helps me to understand what the patient is thinking or is hoping for as an additional benefit to cataract surgery."



Surgeons recommend that you think of the referring OD as part of your team.

There are several keys for making the patient evaluation more efficient—starting with clear guidelines and getting your staff on board with those guidelines. "The staff should be aware of all of the lens choices and be able to recognize potential candidates for certain types of lens implants based on those guidelines," says Cory Pickett, an ophthalmlic consultant in the Midland, Texas, area.

Mr. Pickett's advice: Start your involvement early on. For example, once pretesting is done, you might review the initial results and perform a preliminary slit lamp exam, explain that the patient has cataracts and instruct the staff which follow-up tests to perform. "It is important the surgeon puts his own spin on that so it doesn't come off as robotic," he adds.

For example, Dr. Chang uses an eye model to demonstrate to patients what happens during cataract surgery and what implant he or she might wish to consider. He also uses an IOL model that shows the difference between monofocal and diffractive lenses.

In Dr. Wallace's practice, two technicians who serve as IOL counselors meet with patients after he finishes his examination. These counselors refer prospective candidates to the staff optometrist or perform further testing themselves to determine if any factors might make the patients unsuitable for premium IOLs. They also review the brochures the patient was sent to answer any questions the patient or family members may have, then show them their options and discuss pricing.

This brings up two additional points. First, think of the referring optometrist as part of your team. "One of the values of having referring optometrists is that they know the personality traits of the patient better than we do," Dr. Wallace says.

They also know based on their own findings who may be a good candidate for a premium IOL and any history that might make the patient unsuitable, such as a history of RK or PRK. And the referring optometrist can let the patients know which options you'll likely discuss when the patient is in your chair. "It helps to use a group effort to find out which patients are good candidates," Dr. Wallace says.

Second, consider delegating discussions of cost to your staff. "Most of the time I try not to talk about cost," Dr. Chang says.

Instead, he has his surgical coordinator discuss cost and financing options with the patient—another way of reminding him or her that premium IOLs aren't covered by Medicare. Given that some patients will not consider options that aren't covered, this is a time-saver for the doctor.

The Technology Advantage

In addition to your staff's help, continue to take advantage of diagnostic technology to guide your exam. Just as IOL technology has evolved—and continues to evolve—so, too, has diagnostic technology. "Another way to expedite the evaluation is by using this technology to find out information quickly," Mr. Picket says.

For example, Mr. Pickett recommends the OPD-Scan III Wavefront Aberrometer (Marco), which essentially serves as autorefractor, keratometer, pupillometer (up to 9.5 mm), corneal topographer and integrated wavefront aberrometer. "You get this information quickly and have a basic idea of what the patient may be a candidate for very

early in the evaluation," he says. "This can be used to help guide the rest of the exam," he says.

To narrow down in advance which lenses might be appropriate for the patient, look at the information you have in hand, including:

• ***Ocular surface health***. Blurred vision postop and ocular surface issues, often the result of pre-existing dry eye, are among the major causes of patient dissatisfaction after an implant with a multifocal IOL. "If they have keratitis present, with dry eyes, and/or meibomian gland dysfunction, this must be treated before considering a multifocal IOL," says Dr. Colvard. "If the findings persist despite treatment, I try to lead patients away from multifocal IOLs."

• ***Macular health.*** "The first thing I consider when I begin to review options with the patient is the presence or absence of macular pathology," Dr. Colvard says. "If macular issues exist, I show the patient the OCT, explain the implications, and guide the patient away from IOLs with multifocality. Macular degeneration, epiretinal membranes—any kind of macular pathology—will reduce the patient's contrast sensitivity."

• ***Corneal topography.*** Research has shown that toric IOLs provide better uncorrected vision, greater spectacle independence, and lower residual astigmatism than non-toric IOLs, even with relaxing incisions.[1]

"If the corneal map shows -2 D of astigmatism, I'll only talk toric lenses," Dr. Loden says. "So it narrows my choices down before I even come in. If the eye looks healthy and patient says, 'I'm interested in these options,' then we go into the lenses."

Dr. Colvard discusses toric IOLs if the patient has more than -1 D of astigmatism. "If the patient has an astigmatic error greater than -1 D, I explain the significance of this and explain that we have two options with new technology to correct astigmatism and improve vision without glasses," adds Dr. Colvard.

Invest the time

Obviously, the IOL selection process involves a lot of information for the patient to assimiliate. "It's sometimes a lot for doctors to assimilate, too," Dr. Loden says.

Accept that you'll need to spend more time than you did 10 years ago, when there were fewer options. But, in those extra minutes, you'll be able to satisfy the patient's visual needs and grow your practice—more than you might have been able to do with standard monocular IOLs several years ago. "You'd have to do five cataracts minimum to make up that difference," Dr. Loden says. REVIEW

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Surgeons Tune in To the Symfony

Walter Bethke, Editor in Chief

New technology may encourage surgeons to give premium IOLs a second look.

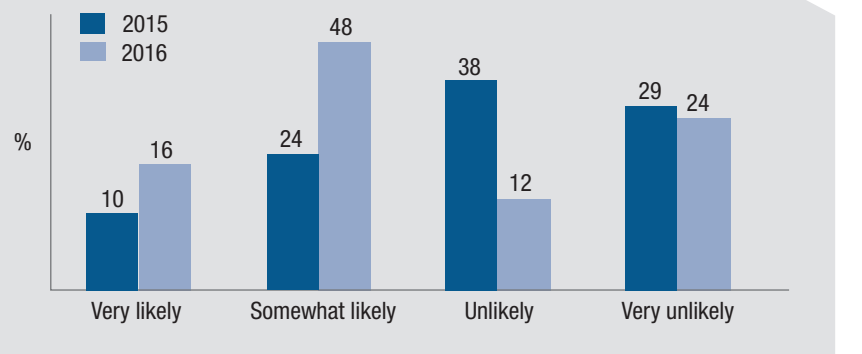
As recently as last year's intraocular lens e-survey, cataract surgeons seemed hesitant to embrace presbyopic IOLs wholeheartedly, and, in their survey comments, would often say that their interest in the devices might be higher if some different technology came along. Even though it's only the responses from one questionnaire, if this month's IOL e-survey is any indication surgeons may have found that different technology in the form of the Abbott Symfony IOL. The arrival of this new lens appears to have rekindled surgeons' interest in giving patients a wider range of vision via an IOL, with the reasons for their renewed interest ranging from the possibility 0f a lower rate of qualitative vision problems to the simple fact that the Symfony addresses astigmatism as well as depth of focus.

In addition to documenting their outlook on presbyopic lens options, surgeons responding to this month's IOL survey also shared their opinions on topics such as the most important features for an IOL to have, toric IOLs and managing complications of IOLs that require a secondary procedure to suture-fixate the lens. This month, the e-mail survey was opened by 1,089 of 8,171 subscribers to *Review*'s e-mail service (13.3 percent open rate) and, of those, 74 shared their responses. To see how your opinions on IOLs compare with theirs, read on.

Growing Interest

In last year's IOL survey, surgeons

Surgeons' Likelihood of Using a Presbyopic IOL in Two Years



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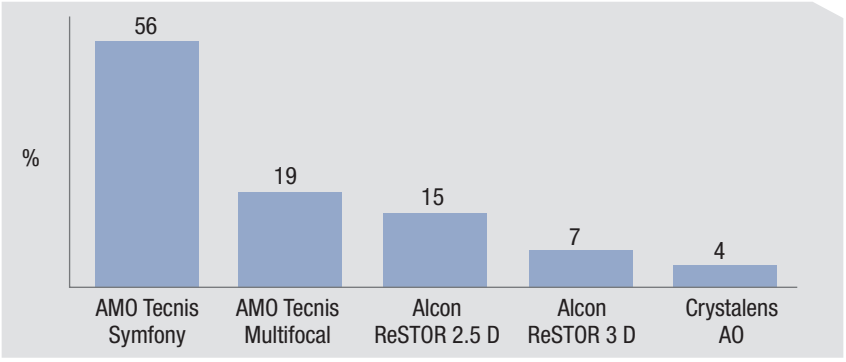
didn't have high hopes for presbyopic lenses: 38 percent characterized themselves as unlikely to use a presbyopic IOL within two years, and 29 percent said they were very unlikely to do so (for a total of 67 percent in the negative). Only 24 percent said they were somewhat likely to try them, and just 10 percent were very likely.

The First Presbyopic IOL Surgeons Are Most Likely to Try



This year, however, things have nearly flipped, with 48 percent of surgeons saying they're somewhat likely to try presbyopic lenses and 16 percent saying they're very likely (putting 64 percent of the respondents in the positive camp). Twelve percent describe themselves as unlikely to try the lenses, and 24 percent say they're very unlikely. "The presently available multifocal IOLs have too many problems with visual aberrations and quality of vision," says Nick Mamalis, MD, director of the Intermountain Ocular Research Center at the University of Utah's Moran Eye Center. "The 'accommodating' IOLs do not really accommodate. I'm interested to see how the extended depth of focus IOLs work out and will consider using them in the future." A retina surgeon who chose to remain anonymous says he's very likely to use a presbyopic lens in the coming year, but he has reservations. "I understand the Symfony lens may have less effect on contrast sensitivity; I'll research this and, if this is the case, I feel it may be a good option," he says. "Additionally, I feel that surgery for 'dysfunctional lens syndrome' in the presence of clear lenses should be accompanied by full and complete disclosure that cataract surgery in young patients—especially males—is associated with a high risk of vision threatening retinal complications."

Though the overall numerical results were positive, many of the surgeons who described themselves as somewhat likely to use a presbyopic lens maintained a guarded outlook on the devices. "There are still unanswered questions about the night-driving qualities of these lenses," says a surgeon from Kansas.

A surgeon from Ohio is thinking along the same lines. "I hesitate to use a lens that can decrease a patient's best potential visual acuity," he says. "I also hate to risk problems with glare and halos. If a patient has a high priority for being spectacle-free, I will use them. Otherwise, I hate to leave patients with a lens that could impair their best corrected visual acuity and glare for the rest of their, hopefully, many years of future life."

When asked which lens in particular they might like to try if they're not yet performing presbyopic lens surgery, 56 percent of the respondents chose the Symfony. Nineteen percent named the Tecnis multifocal and 15 percent said the ReSTOR 2.5 D. *(The rest of the results appear in the graph above.)* "The Symfony has a longer range of focus and a wider central zone," explains a surgeon from Oregon who says he most likely would try the Symfony. "Also, it takes the patient's astigmatism into account." A surgeon from Michigan also says he might implant the Symfony. "I'd like to try this new lens and see if the results are satisfactory," he says. "Also, I'd like to see if the side effects are less."

As for the surgeons who currently use presbyopic lenses, 34 percent are satisfied with their lens, and 27 percent are very satisfied. Thirty-seven percent say they're somewhat satisfied, while 2 percent are unsatisfied.

"They're not great, but they're all we have," says a surgeon from Maryland who implants the ReSTOR and the Tecnis multifocal. "There is a loss of contrast sensitivity, and we must screen patients carefully prior to use. These lenses can only be used in a small percentage of patients. We need a lens that mimics the natural lens in design."

Sid Moore, MD, of Macon, Ga., agrees that this sort of lens would be helpful. "A true accommodative lens would be hugely beneficial," he says. "Optical compromises with multifocals make predicting patient satisfaction difficult."

A surgeon from Maryland who's begun implanting the Symfony lens says that he's had a positive experience so far. "I love the new Symfony lens," he says. "Minimal halos, great optics. Patients say they have never seen like this before. I'd love it to have a little more reading vision and would also like to have better IOL formulas to improve outcomes." Jon Weston, MD, of Roseburg, Ore., says he's developed a way to deal with any near issues with Symfony. "I'll mix a Tecnis multifocal with a Symfony if sharper vision for shorter working distances is needed," he says.

Surgeons Rank the Features of IOLs

Surgeons on the survey ranked IOL features in terms of their usefulness using a numerical scale that ran from 1 (least useful) to 6 (most useful). The average scores are shown.

Lens Design

Surgeons also took a look at the various elements of IOL design, commenting on which ones they preferred.

In terms of monofocal IOLs, 51 percent of the respondents say they use the Alcon IQ Aspheric for most of their cases, and a third prefer the AMO Tecnis one-piece lens. The rest of the lenses were chosen by less than 5 percent of surgeons. Eighty-five percent of them think acrylic is the best material, with 7 percent preferring silicone.

Surgeons also ranked specific IOL features, such as toric correction or multifocality/bifocality, on a scale of one to six, with six being most important. *(A graph of all the rankings appears above.)* Toric design, with an average rank of 4.5, was thought to be most important, followed closely by asphericity/neutral asphericity at 4.2. Pseudo-accommodative motion, at 2.6, was thought to be least important. "The optics are the most important part of any lens," avers Bruce Cohen, MD, of St. Louis. A surgeon from Montana says he doesn't have a lot of confidence in multifocality/bifocality, saying, "Premium lens patients are a pain if they have the least little complaint after paying extra out of pocket." A surgeon from Maryland also doesn't think highly of this approach to presbyopia. "Right now," he says, "it seems better to correct presbyopia on the cornea than within the lens."

As the rankings suggest, surgeons are very impressed with toric IOLs. Fully 65 percent of surgeons rate toric performance as excellent, and 31 percent say it's good. Fifty-seven percent of the surgeons use the AcrySof toric for most of their cases, and 33 percent use the Tecnis toric. Eight percent use the Symfony. "Toric IOLs provide excellent vision and have been a real advance in the treatment of patients with cataracts and astigmatism," says Dr. Mamalis. Ron Glassman, MD, of Teaneck, N.J., agrees, saying, "This is the way to treat astigmatism."

Some surgeons on the IOL survey, however, are more reserved in their praise for toric lenses, noting that, though they're useful in many cataract cases, they can still have some issues, as well. "Often, there's astigmatism that's unaccounted for in the preop calculations," says a surgeon from Michigan. "Also, the lens often rotates at the last second when trying to remove the viscoelastic." A surgeon from Maryland says, "It's difficult for the patient to go back to the OR if I need to rotate the lens; we also need a better system to ensure alignment in the OR."

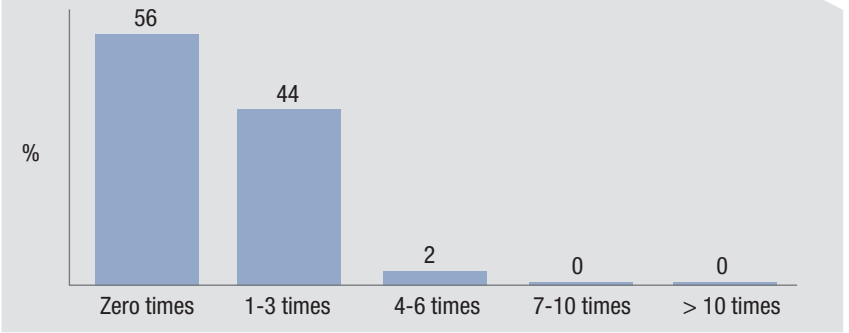
Complications

In another section of the survey, surgeons say there are times when implantations don't go as well as hoped, and intraocular lenses need to be sutured in place in order to remain stable. Fifty-four percent of the respondents, though, say that this is rare, and they don't need to do it in a given year. Forty-four percent, however, say they usually need to suture a lens one to three times per year, and 2 percent have to do it four to six times.

Surgeons also described various scenarios that called for suturing. "Suturing was performed for a dislocated IOL within the capsular bag or for a case of poor zonular support," recounts Dr. Mamalis. A surgeon from Montana says his suturing was a result of "pseudoexfoliation and a dehisced capsular bag," for which he sutured the lens to the iris, adding he'll suture it "rarely to the sclera."

Juan Nieto, MD, of Dubuque, Iowa, says his complicated IOL suturing cases usually involve "poor or no capsular support" and that he's "comfortable suturing to the iris or glueing it to/tucking it into the sclera." An ophthalmologist from Kansas says there's one surgeon at his practice who performs all the challenging cases requiring IOL suturing. "He uses mostly an intrascleral fixation approach for them," he says. "He does fewer cases using either polypropylene suturing to the iris, or Gore-Tex suturing to the sclera." REVIEW

Surgeons' Annual Frequency of Suturing an IOL



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(Continued from p. 4)

"Despite these exciting findings, there are a few limitations to this system," Dr. Peng notes. "The algorithm may not perform as well for images with subtle findings that a majority of ophthalmologists would miss. Another limitation arises from the nature of deep networks, in which the neural network was provided with only the image and associated grade, without explicit definitions of features (microaneurysms, exudates). Because the network 'learned' the features that were most predictive, it is indeed possible that the algorithm is using features previously unknown to or ignored by humans. Understanding which features are used to make predictions will be an important area of investigation for further studies, and is indeed an active area of research within the larger machine-learning community."

Fovista Fails to Meet Phase III Endpoint

Hot on the heels of apparently positive data from its Phase IIb trial, the platelet-derived growth factor drug Fovista (Ophthotech) didn't provide the visual acuity benefit that was aimed for in its pivotal Phase III study.

The Phase III Fovista clinical trials, OPH1002 and OPH1003, were international, multicenter, randomized, double-masked, controlled studies evaluating 1.5 mg of Fovista administered in combination with Lucentis, an approach dubbed "Fovista combination therapy," compared to Lucentis injection alone, for the treatment of wet age-related macular degeneration. In each trial, patients were randomized to one of two approximately equal sized treatment groups. The two Phase III trials enrolled 1,248 patients with wet AMD.

In data released by Ophthotech, patients receiving Fovista combo therapy gained a mean of 10.24 letters at 12 months compared to a mean gain of 10.01 letters for patients receiving Lucentis monotherapy. In OPH1002, consisting of 619 patients, combo-therapy patients gained a mean of 10.74 letters at 12 months, compared to a mean gain of 9.82 ETDRS letters in Lucentis-only patients. In OPH1003, consisting of 626 treated patients, subjects receiving combo therapy gained a mean of 9.91 letters at 12 months vs. a mean gain of 10.36 ETDRS letters in patients receiving Lucentis monotherapy. None of these results of the pre-specified primary efficacy analysis were statistically significant, the researchers say.

In a pooled data analysis, 12.1 percent of patients receiving combo therapy lost five or more letters from baseline at one year, compared to 11.2 percent of patients receiving Lucentis alone. In OPH1002, 12 percent of patients receiving the combination lost five or more letters at month 12, compared to 12.3 percent of patients receiving Lucentis. And in OPH1003, 12.2 percent of patients receiving the Fovista combination lost five or more letters at a year, compared to 10.2 percent of the Lucentis patients.

Samir Patel, president of Ophthotech, expressed his disappointment in the results in a conference call following the release of the data. "We are in the process of analyzing the data in order to better understand this outcome," he said. "We are most disappointed by these results—especially for patients." REVIEW

News Briefs

• *BromSite now available.* Sun Pharma recently made the non-steroidal anti-inflammatory drop BromSite available for sale. Approved in April 2016 by the FDA, BromSite (bromfenac ophthalmic solution) 0.075% has unique labeling: It's the first NSAID approved for the actual prevention of ocular pain that follows cataract surgery, as well as the postoperative treatment of inflammation. Sun also notes that it's the first bromfenac ophthalmic solution formulated in DuraSite, a polymer-based drug delivery system used to improve drug solubility, absorption, bioavailability and residence time. The product will be marketed by Sun Ophthalmics.

In terms of safety, the company notes that, like other NSAIDs, there is a potential for cross-sensitivity with BromSite, and the potential for increased bleeding time of ocular tissue due to interference with platelet aggregation. In addition, Sun notes that BromSite should not be administered while a contact lens is in the eye, as soft lenses may absorb the drug's preservative, benzalkonium chloride.

Regarding adverse events, the most commonly reported adverse reactions, occurring in 1 to 8 percent of patients, were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

For more information on the new NSAID, visit bromsite.com.

• *New swept-source OCT approved.* Carl Zeiss Meditech says its newly approved PLEX Elite 9000 offers swept-source OCT posterior ocular imaging. The company claims that the new OCT imaging method will expand the potential for researchers to easily diagnose diseases affecting the retina.

ZEISS highlights the wide-field, high-resolution visualization provided by the new imaging of the PLEX Elite platform, allowing clinicians to examine microstructures and microvasculature at any depth, from vitreous to sclera. Zeiss says the examination of these microstructures offers researchers the potential to explore the progression of retinal and choroidal pathology, to study choroid physiopathology, and to evaluate how the retina and choroid respond to therapy.

ZEISS notes that the new PLEX Elite 9000 will have a limited release for use as a research tool.

For more information on ZEISS' new OCT, visit zeiss.com.


The Clinical Utility of OCT Angiography

Retina specialists experienced in OCTA discuss the strengths—and the limitations—of this promising new technology.

Eduardo Novais, MD, Sao Paulo, Brazil, and Caroline Baumal, MD, Boston

The retinal and choroidal vasculature can be the site of pathology in many ocular diseases, and dye-based angiography has been the gold standard diagnostic test for assessing vascular disorders such as choroidal neovascularization, retinal vascular occlusion, diabetic retinopathy, macular telangiectasia and central serous chorioretinopathy.[1,2] Though dye-based approaches such as fluorescein angiography and indocyanine green angiography allow for direct visualization of the dynamic properties of vascular flow such as leakage, pooling or staining, they're not without limitations: Visualization of small vascular details can be difficult, since they may become obscured due to late-phase dye leakage. Furthermore, dye-based tests are time-consuming, require intravenous access and have the potential for systemic side effects, including rare reports of anaphylaxis.[3] Optical coherence tomography angiography is a novel imaging technique that may be able to overcome some of the limitations of dye-based approaches—though it has some limitations as well. In this article, we'll discuss the clinical utility of OCTA.

OCTA Explained

OCTA is a noninvasive imaging modality that allows for detection of blood flow and three-dimensional reconstruction of blood vessels using signal decorrelation between consecutive transverse cross-sectional OCT scans. An OCTA image is computed by comparing, on a pixel-by-pixel basis, repeated B-scans acquired at the same retinal location in rapid succession. The rationale behind OCTA imaging is that in non-mobile tissue the reflected signal will be stationary, and thus the repeated B-scans will be identical. Inside vasculature, however, moving erythrocytes cause a time-dependent backscattering of the OCT signal, which manifests as differences among the repeated B-scans.[4-6]

Basically, OCT angiograms of the posterior pole can be obtained by using one or a combination of two methodologies: amplitude decorrelation and phase-variance. Amplitude decorrelation analyzes amplitude changes in the OCT signal. Split-spectrum amplitude decorrelation partitions the spectrum into smaller spectra and performs the repeated B-scan decorrelation separately for each sub-spectrum, which improves the signal-to-noise ratio.[7] Doppler OCT is a phase-based technology from which OCTA has its origins.[8,9] It can quantify axial blood flow that's parallel to the direction of the imaging acquisition device.[7,10,11]

In addition, it's possible to view OCTA images in tandem with the corresponding structural en face and cross-sectional OCT B-scans. This allows the correlation of clinical and structural features of retinal and choroidal diseases with microvascular features seen on OCTA.

OCTA for Vascular Disease

The retinal capillary network is arranged into morphologically distinct layers. The superficial retinal capillary plexus is located predominantly within the ganglion cell layer; and the deep retinal capillary plexus is located at the outer boundary of the inner nuclear layer, with a smaller intermediate retinal capillary plexus at the inner margin of the inner nuclear layer. The vascular layers of the retina are connected by perpendicularly positioned vessels.[12] With the ability to analyze each vas-

This article has no commercial sponsorship.

cular plexus separately, OCTA has become an important tool for studying retinal vascular diseases such as MacTel, RVO, DR and others. For example, OCTA was used to demonstrate that the superficial and deep retinal capillary plexuses may be affected differently by retinal vascular diseases such as retinal artery and vein occlusion.[13-15]

Another advantage of OCTA is its superior ability to precisely delineate the vessels surrounding the foveal avascular zone *(See Figure 1)*. In contrast, perifoveal leakage of fluorescein dye may blur the FAZ margins, and FA is limited to primarily delineating the superficial vascular plexus. Increased FAZ size has been correlated to reduced visual acuity prognosis in eyes with retinal vascular disease.[16] A recent study demonstrated that the perifoveal intercapillary area on OCTA appears to increase in size as the level of diabetic retinopathy progresses.[17] Also, neovascularization of the optic nerve, which can occur in proliferative DR and ischemic retinopathy, can be easily detected using OCTA by viewing the inner retina/optic nerve surface at the most superficial level *(See Figure 2)*.[18]

It's been hypothesized that OCTA may show retinal microcirculation impairment in the macula prior to the development of retinopathy.[19] One study demonstrated that diabetic individuals without clinical evidence of diabetic retinopathy have larger FAZ sizes as well as FAZ remodeling and subtle capillary non-perfusion compared to normal, non-diabetic control eyes.[20] Microaneurysms imaged with FA may not always be apparent on OCTA. This may result from stagnant erythrocytes blocking flow, or the flow in the microaneurysms may be below the threshold of detection of OCTA. Microaneurysms on FA may also correspond to capillary loops or preretinal neovascular tufts on OCTA.[21]

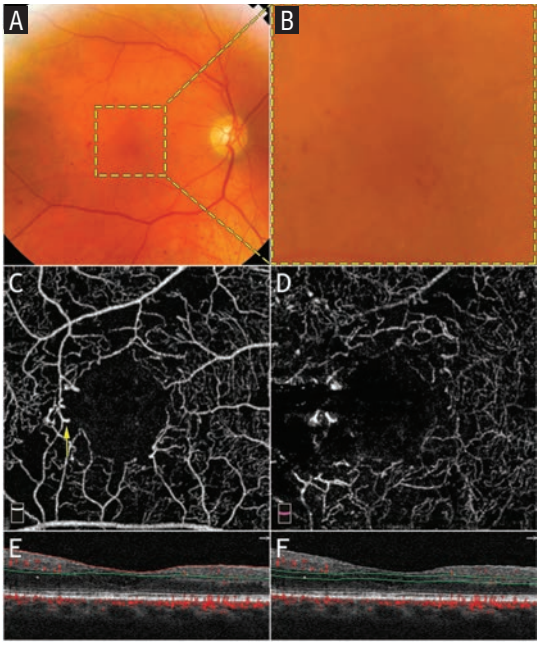

Figure 1. Multimodal imaging of a 65-year-old patient with moderate non-proliferative diabetic retinopathy. (A) Color photograph shows intraretinal blot-dot hemorrhages and microaneurysms. (B) Yellow-dashed frame identifies the corresponding 3x3-mm area imaged on OCTA. (C) OCTA segmented at the superficial retinal plexus shows an enlarged foveal avascular zone (FAZ). Microaneurysms can also be easily identified (yellow arrow). (D) OCTA segmented at the deep retinal plexus shows further enlargement of the FAZ. (E) and (F) represent corresponding OCT B-scan segmentation of the superficial and deep plexuses, respectively, with decorrelation signal overlay.

OCTA for Chorioretinal Disease

Evaluation of CNV using OCTA is one of the most important applications of this modality.[4,22,23] OCTA can be used to determine the location of the CNV, its morphology and its response to anti-VEGF therapy. As a baseline, in a normal eye the "outer retina" OCTA scan segmenting between the outer plexiform layer and Bruch's membrane will be devoid of signal, as there's no vascular flow in this layer. However, this may not be the case in eyes with CNV.

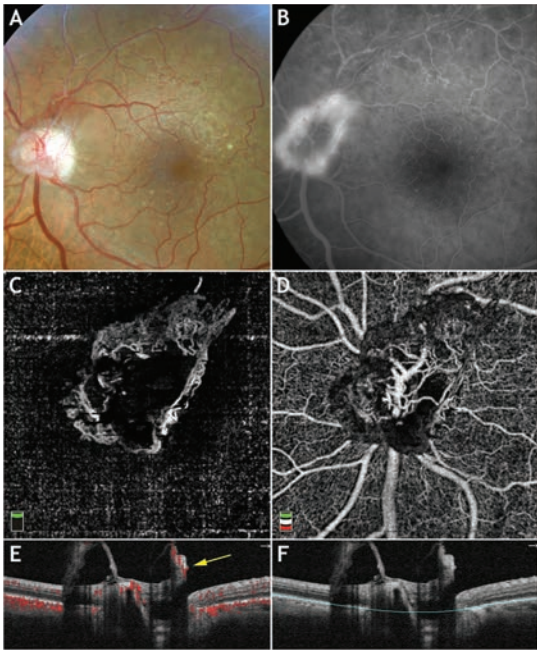

Figure 2. Multimodal imaging of a 60-year-old patient with superotemporal branch retinal vein occlusion. (A) Color photograph shows neovascularization of the disc. (B) Late-phase FA shows hyperfluorescence of the optic nerve due to neovascularization leakage. Optical coherence tomography angiography of the vitreous (C) and optic nerve head (D) demonstrates some well-delineated, fine, abnormal vessels. (E) and (F) represent corresponding OCT B-scan segmentation of the optic nerve head and vitreous. The yellow arrow points to the presence of the decorrelation signal on the vitreous interface, indicative of neovascularization flow.

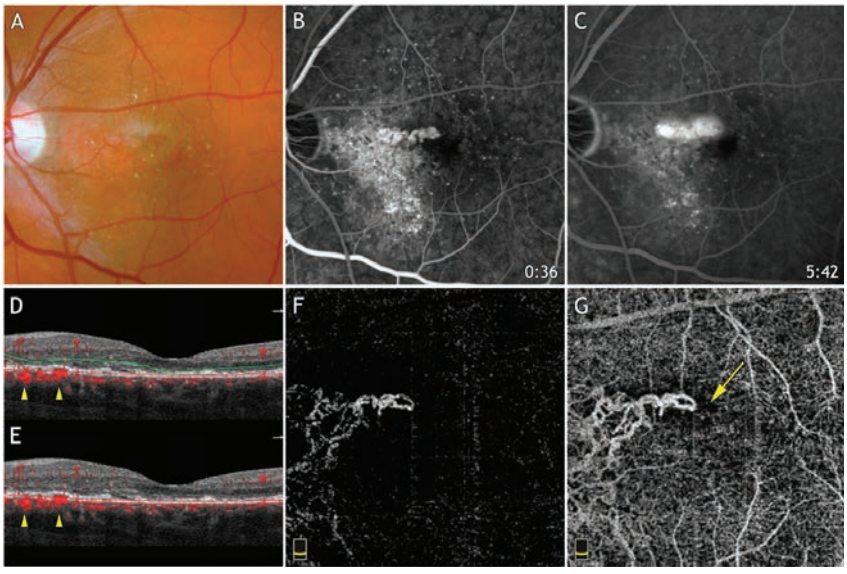

Figure 3. Multimodal imaging of a 63-year-old patient with choroidal neovascularization secondary to central serous chorioretinopathy. (A) Color photograph shows a subretinal hemorrhage at the center of the macula surrounded by retinal pigment epithelium clumps. Early (B) and late-phase (C) fluorescein angiography show leakage from CNV. (D) and (E) represent corresponding OCT B-scan segmentation of the outer retinal and choriocapillaris, respectively. Yellow arrowheads point to the decorrelation signal below the RPE detachment suggestive of CNV. (F) OCT angiogram segmented at the level of the outer retina reveals CNV. (G) OCT angiogram segmented at the level of the choriocapillaris. The yellow arrow highlights the hypo-intense halo surrounding the CNV.

There are different CNV morphologies on OCTA, but the clinical relevance of this is yet to be determined. CNV can be identified as several small filamentous vessels that form anastomoses (known as "seafan" or "lacy-wheel"), or as vessels associated with a central trunk of vessels ("Medusa") *(Figure 3)*. Recently, researchers analyzed OCTA patterns of CNV and their potential correspondence to quiescent and progressive CNV characteristics seen on multimodal imaging (FA, IGCA and spectral-domain OCT). In this study, the investigators imaged CNV using OCTA and graded it according to the presence or absence of the following features: well-defined CNV; presence of tiny capillaries; presence of anastomoses and loops; morphology of the vessels termini as opposed to a "dead tree" aspect; and presence of a hypointense halo surrounding the CNV. They found a 95-percent agreement between OCTA and the traditional multimodal imaging protocol for a "treatment required" decision in eyes with at least three out of the five features. There was a 91-percent agreement for "treatment not required" when patients presented with fewer than three features.[24]

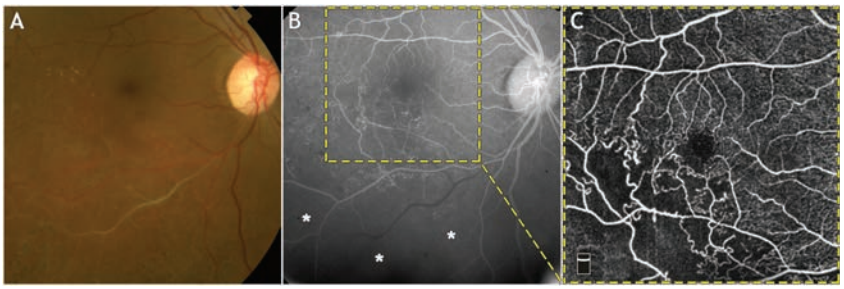

Figure 4. Multimodal imaging of a 54-year-old patient with branch retinal vein occlusion of the inferior temporal arcade. (A) Color fundus photography shows non-perfused vessels and hyperpigmented laser scars on the inferior temporal retina. (B) Fluorescein angiography. Yellow-dashed frame identifies the corresponding 6x6-mm area imaged on optical coherence tomography angiography. White asterisks denote an ischemic retina not captured due to the small-field coverage. (C) En face OCTA segmented at the superficial retinal plexus shows a non-perfused area of the retina temporal-inferior to the fovea.

Depending on the clinical presentation, OCTA's sensitivity to visualize abnormal vascular networks may vary. When massive hemorrhage, exudate or fibrotic tissue is present, OCTA signals can be blocked, limiting visualization of CNV. Because CNV secondary to chronic CSCR and myopic CNV are rarely associated with large subretinal hemorrhages that limit penetration of the OCT signal, the abnormal vascular network may be identified with a screening OCTA in such cases.

Choroidal neovascularization can be classified according to the abnormal vascular plexus location in various retinal and choroidal layers: below the retinal pigment epithelium (type 1 CNV); above the RPE (type 2 CNV); and intraretinal (type 3 CNV). On OCTA, CNV classification depends on where the evidence of a vascular decorrelation signal is located. It can be located immediately above the RPE (type 2 CNV), and between Bruch's membrane and the RPE (type 1 CNV).[24] Since there can be OCT signal attenuation from the RPE-Bruch's membrane complex,[25,26] it's possible that visualization beneath the RPE may influence the type 1 CNV identification. Thus, differences in signal penetration may play an important role in this imaging modality.

SD vs. SS OCTA for CNV

There are currently three FDA-approved OCTA systems. Two of them use a spectral-domain platform operating at ~840-nm wavelength. The third uses swept-source OCTA technology with a longer ~1050-nm wavelength and is in limited commercial release in the United States. It's possible that SS-OCTA may be less affected by ocular opacity and allow a deeper penetration into the choroid.[25-28]

SS-OCTA also has less variation in sensitivity with depth (sensitivity roll-off) compared to SD-OCTA. In SD-OCTA, the imaging system is most sensitive to signals coming from reflectors close to what is known as the zero-delay line; as a reflector is moved away from the zero-delay, the system becomes less sensitive to the back-reflected signals.[29] This sensitivity roll-off is due to the limited spectral resolution of the spectrometers that are used in SD-OCTA systems. In contrast, SS-OCTA systems don't use spectrometer-based detection. Instead, in SS systems, it's the instantaneous linewidth of the swept light source, along with the analog-to-digital acquisition rate, that determine the sensitivity roll-off of the system. This difference enables SS-OCTA systems to have improved sensitivity roll-off compared to SD-OCTA systems,[30] which improves visualization of the choroid both on cross-sectional as well as en face OCTA imaging, and may also improve visualization of CNV, especially the sub-RPE component of the membrane.[31]

Limitations of OCTA

There are some limitations to OCTA imaging in its current configuration. One drawback is its restricted field of view *(See Figure 4)*. The automated scan protocols that are currently available are 2x2 mm, 3x3 mm, 6x6 mm and 8x8 mm. In order to generate an OCT angiogram, OCT scans need to be repeated at least twice at each position in a volumetric raster scan. However, since the number of cross-sectional OCT scans is limited by the scanning speed of the instrument, a larger field of view will have reduced density and resolution.

OCTA is prone to several artifacts during acquisition or post-acquisition image processing. In order to interpret OCTA images, it's necessary to be aware of the potential image artifacts that can occur so as not to interpret these as part of the actual anatomy. OCTA works by detection of erythrocyte motion, so any extraneous movement during the image-capturing process may result in motion artifacts, which appear as white or black lines in the flow angiograms, and/or misalignment of the retinal vasculature. Additionally, superficial vessels may erroneously appear in segmented views of deeper layers, such as the outer retina and choriocapillaris.[32] These are termed "projection artifacts," and may lead to incorrect diagnosis if not promptly identified (i.e., the retinal vessels' projection may be misinterpreted as CNV).

Another issue is that commercially available OCTA devices are currently expensive, although this may change as the technology becomes more common. Also, there is currently no code beyond the standard OCT imaging code with regards to reimbursement. Finally, in terms of utility, while OCTA provides additional clinical information for the practitioner, such as noninvasive identification of CNV and retinal vascular abnormalities, its usefulness with regards to therapeutic monitoring is unclear.

FA and ICGA demonstrate the dynamic properties of dye within vascular networks, such as leakage in disorders that produce vascular incompetence and exudation, and dye-based angiography is still an important tool for diagnosis and management of chorioretinal diseases, especially when assessing the periphery of the fundus. OCTA is a promising technology, however, as it allows simultaneous assessment of both structural and vascular flow. OCTA is also safer, faster, more easily repeated and more comfortable for the patient than dye-based angiography, and it may provide more detailed information about blood flow in retinal and choroidal vasculature. The ability to rapidly obtain images of vascular plexuses and assess the integrity of retinal and choroidal perfusion should prove invaluable as a screening and diagnostic strategy for chorioretinal disorders. REVIEW

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The Many Shades Of Pinkeye

A discussion of the various causes of conjunctivitis, and new therapeutic approaches on the horizon.

Mark B. Abelson, MD, CM, FRCSC, FARVO, Aron Shapiro, Connie Slocum, PhD, and David A. Hollander, MD, MBA, Andover, Mass.

Nowhere do the practices of primary care medicine and ophthalmology overlap more than in the diagnosis and treatment of conjunctivitis, the pathological inflammation of the conjunctiva. The condition presents itself in many forms; it can be due to infectious agents, allergens, chemical or irritant exposures, or physical trauma.

In Western countries, infectious conjunctivitis is common, with an incidence of 15 per 1,000 patients per year in primary care.[1] Although most incidents of conjunctivitis are treated in the primary care setting, complications from viral or bacterial infection can arise and lead to sight-threatening conditions.[2] Conjunctivitis is also a major health issue in developing countries, especially in areas with poor public water supplies. Outside the United States, cases of conjunctivitis are estimated to affect more than 30 million people, due to both the highly contagious nature of infectious forms and to poor sanitary conditions that lead to cycles of repeated infection. An example of this is trachoma, a bacterial conjunctivitis that is the most preventable cause of blindness worldwide; it's estimated to be responsible for ~2 million cases of blindness or visual impairment.[3] While rare in the United States, the devastating effects of trachoma and other conjunctival infections serve to remind us that these seemingly innocuous ailments can have serious complications. This month we examine the current standard of care and emerging trends in this all-too-common ocular malady, with a particular focus on viral forms of the disease.

Identifying Infectious Agents

Infectious conjunctivitis is particularly prevalent in the pediatric population, where one in eight schoolchildren is expected to have an episode each year.[4] The contagious nature of these infections means that children diagnosed with "pinkeye" are required to leave school and seek treatment. Indeed, cases of conjunctivitis have been shown to be the leading cause of day care and school absences, which directly impacts a parent's time at work.[5] Outbreaks tend to be rapid and pervasive, owing to the extremely contagious nature of the condition; the importance of rigorous hygiene cannot be overemphasized in these situations. This aspect of the disease leads to a major impact on productivity through losses of time at work and medical visits that represent a significant economic burden for society.

Patients presenting with infectious conjunctivitis typically experience a bilateral hyperemia along with other signs such as ocular discharge, tearing, chemosis, itching, pain or irritation. Some patients may also experience lid edema or photophobia, petechial hemorrhage, follicles on the tarsal or fornix conjunctiva, and preauricular lymphadenopathy.[6-9] Other signs associated with a viral rather than bacterial infection are palpable pre-auricular or submandibular lymph nodes.[7] Viral infections may also produce follicles caused by a lymphocytic response of the conjunctiva.[7] It's important to note that these follicles are different from papillae, which are formed by bunches of conjunctival capillaries that become dilated during some other ocular diseases such as giant papillary conjunctivitis.

While there are many signs and symptoms that overlap between bac-

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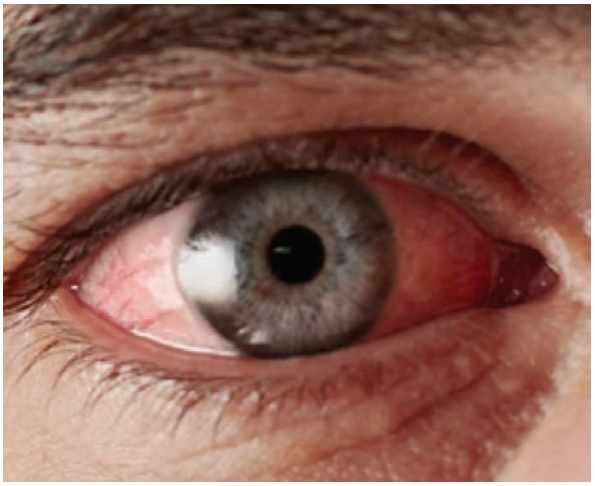
terial and viral forms of conjunctivitis, the nature of the discharge is typically the key diagnostic characteristic: To differentiate between viral and bacterial forms of conjunctivitis, it's generally accepted that a thick, purulent discharge is associated with bacterial conjunctivitis, while a watery discharge is more characteristic of viral conjunctivitis.[7,8] Specifically, if the eye exhibits a sticky, opaque secretion, then a bacterial infection is most likely; without this, a viral infection is most probable. Laboratory tests confirming these diagnoses are not usually required, but a culture swab of the conjunctiva prior to initiation of treatment may be useful.[10] The use of an in-office rapid antigen test can help prevent the inappropriate use of antibiotics, due to its accuracy in identifying a viral infection from a group of viruses—adenoviruses—which comprise 65 to 90 percent of all viral conjunctivitis cases.[10] The in-office antigen test has been shown to be highly specific (~95 percent), although the reports of test sensitivity have been more variable.[11,12] The value of these tests is that they prevent the unnecessary use of antibiotics, which have no value in our therapies for viral infections.

Although many patients visit a physician with the hopes of receiving a treatment for quick recovery, there is currently no specific treatment for the viral form of infectious conjunctivitis. Treatment typically involves the use of cold packs, artificial tear lubricant eye drops, ocular decongestants and education on preventing transmission of the virus through frequent handwashing.[10,13] For the most part, antivirals have been shown to be ineffective in treating viral conjunctivitis; the exception to this is in the case of herpes simplex viral infections, which comprise between 1 and 5 percent of all acute conjunctivitis cases. Antivirals such as acyclovir, trifluridine and valacyclovir have all been shown to effectively treat herpesvirus infections.[9]



Steroid treatment in the setting of viral conjunctivitis may increase the latency of the virus, prolonging the infection.

While corticosteroids are often prescribed to dampen inflammation associated with a number of ocular disorders, the use of steroid monotherapy in the treatment of viral conjunctivitis isn't currently recommended. It's been shown that steroid treatment, even for a short period of time, may actually extend the period of viral shedding and/or increase latency of the virus, consequently prolonging the course of the infection.[7] It's thought that steroids may have this effect on the viral infection due to their interaction with cellular processes associated with the immune system, thus preventing the immune cells from fully eradicating the virus. Combination products such as FST-100 (Shire) that include both a steroid and an anti-infective agent (povidone iodine) may allow for the benefits of steroids without concerns of prolonged disease duration.

Aedes aegypti, the mosquito that carries the Zika virus. Among its many other signs and symptoms, Zika can also cause conjunctivitis in infected individuals.

Beyond Adenovirus

Although the majority of viral infections are due to members of the adenovirus family, there is a tremendous diversity in the types of viruses that infect the eye.[13] There are more than 40 types of adenovirus that cause conditions including colds, gastrointestinal illness, conjunctivitis or more serious ocular conditions. Ocular manifestations of adenoviral infections include pharyngoconjunctival fever, epidemic keratoconjunctivitis, acute nonspecific follicular conjunctivitis, and chronic kerato-conjunctivitis. Other viruses known to cause conjunctivitis include the human immunodeficiency virus, Varicella zoster virus and Epstein-Barr virus.[12,13]

Another virus that has been the subject of much public debate in the past year is the Zika virus.[14] Zika is a mosquito-borne RNA virus, related to viruses associated with dengue fever, yellow fever and West Nile virus. The

virus gained public attention during the Brazil Olympics because of its association with congenital abnormalities in infants of infected mothers. Most patients infected with Zika are asymptomatic, but those infected individuals who display disease features experience a constellation of symptoms including conjunctivitis, fever, maculopapular rash and joint pain.[14] Although the disease is still rare in the United States, increased Zika incidence rates in some southern states suggest that Zika infection may need to be considered as a possible cause for cases of conjunctivitis of unknown etiology that occur in those regions.

Beyond its association with conjunctivitis, a mouse model of Zika demonstrated that the virus was present in the tears, suggesting that Zika might be secreted from the lacrimal gland or shed from the cornea.[15] Additionally, it was shown that Zika infected the iris, retina and optic nerve, leading to panuveitis and neuroretinitis in addition to conjunctivitis. These observations are reminiscent of another recent viral epidemic, the West African Ebola outbreak of 2014. Of course, Ebola is much different from Zika: It is a hemorrhagic fever virus spread without an insect vector, and it primarily impacts the gastrointestinal system, where it is often fatal without significant supportive care. Despite these differences, a well-documented case of an Ebola survivor reported that a convalescing patient presented with uveitis;[16] subsequent to this, follow-up identified 57 Ebola survivors with uveitis, suggesting that infectious virus or viral RNA in the eye may have triggered this complication.[17] It may be that some aspects of ocular physiology leave the eye susceptible to viral infiltration and/or retention, and thus any viral conjunctivitis may have this same risk.

The life cycle of viruses involves an intracellular growth and assembly phase and a cell lysis phase where newly-formed viruses are released to infect other cells. This type of life cycle means it's more difficult to clear a viral infection once it has been introduced; some viruses lay dormant in a nonproliferative stage within the host cell, further extending their inhabitance. These host-pathogen interactions, along with the highly genetically diverse group of viruses that can induce conjunctivitis, have complicated the discovery of effective therapeutics for viral infections.

A mouse model of the Zika virus suggested that it might be secreted from the lacrimal gland or shed from the cornea.

A promising new therapeutic approach to treatment of viral conjunctivitis is represented by OKG-0301 (Okogen, Encinitas, Calif.). While most antiviral drugs act by inhibition of nucleic acid biosynthesis, OKG-0301 is a ribonuclease that acts to inhibit viral replication by interfering with viral protein synthesis. OKG-0301 also interferes with the inflammatory response by inhibiting NF-κB, a transcription regulator that is a key signal point in the inflammation process. Another new product in development, APD-209 (Adenovir Pharma; Helsingborg, Sweden), is designed to treat epidemic keratoconjunctivitis by preventing adenoviral binding and entry into cells. These examples of new therapies are particularly exciting because they represent new mechanistic strategies in the design of antiviral drugs.

The silver lining of these recent viral epidemics is that they rekindle the experimental fires, giving a much-needed boost to research into new antiviral therapies. Hopefully this renewed interest will lead to more effective ways to treat and eliminate all viral conditions, including ocular viral infections. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Mr. Shapiro is vice president at the ophthalmic consulting firm Ora. Dr. Slocum is a medical writer at Ora. Dr. Hollander is chief medical officer at Ora, and assistant clinical professor of ophthalmology at the Jules Stein Eye Institute at the University of California, Los Angeles.

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Understanding the Risk Factors for NAION

Using the Clinformatic DataMart database, researchers sought to understand the risk factors for nonarteritic anterior ischemic optic neuropathy, a devastating ocular disease that causes permanent vision loss. In order to isolate and explore NAION's risk factors, researchers specifically looked at associated demographic, systemic and ocular factors.

This retrospective, longitudinal cohort study included patients between 40 and 75 years old without NAION at baseline who were enrolled in a large U.S. managed-care network. These enrollees were monitored for at least two years between 2001 and 2014 to identify those newly diagnosed with NAION. All persons were under ophthalmic surveillance, and all cases had ≥1 confirmatory ICD-9-CM code for NAION during follow-up.

Of the 1,381,477 eligible enrollees, 977 (0.1 percent) developed NAION during a mean ±standard deviation follow-up of 7.8 ±3.1 years. The ±D mean age for NAION cases at the index date was 64.0 ±9.2 years vs. 58.4 ±9.4 years for the remainder of the beneficiaries. Female subjects had a 36-percent decreased risk of developing NAION compared with male subjects. Compared with whites, Latinos had a 46-percent decreased risk of developing NAION, whereas African ancestry was not significantly associated with NAION. Systemic diseases associated with NAION included hypertension and hypercoagulable states. Although diabetes mellitus was not significantly associated with NAION when compared with those without DM (p=0.45), patients with end-organ involvement from DM had a 27-percent increased risk of NAION relative to those with uncomplicated DM. Ocular diseases associated with NAION were age-related macular degeneration and retinal vein occlusion.

The study identified several modifiable risk factors that may be associated with NAION. Should future studies confirm these findings, they may offer opportunities to prevent or treat this debilitating condition, the researchers say.

Ophthalmology 2016;123:2446-2455

Cestari D, Gaier E, Bouzika P, Blachley T

Air Pollution and Central Retinal Artery Occlusion

Researchers investigated whether daily changes in ambient air pollution were associated with an increased risk of central retinal artery occlusion, using the Taiwan National Health Insurance Research Database.

This retrospective, population-based, cohort study identified patients newly diagnosed with CRAO between 2001 and 2013 in a database of 1,000,000 patients that were randomly selected from all registered beneficiaries of the National Health Insurance program in Taiwan. The researchers referenced air pollutant monitoring stations located near these patients' residences throughout Taiwan to determine the recorded concentrations of pollutants. Patients without corresponding monitoring stations were excluded.

Using a time-stratified, case-crossover study design and conditional logistic regression analysis, researchers assessed associations between the risk of CRAO and the air pollutant levels in the days preceding each increase in those levels. Ninety-six patients with CRAO were enrolled in this study. The mean age was 65.6 years, and 67.7 percent of the patients were male.

The risk of CRAO onset was significantly increased during a five-day period following a one-part-per-billion increase in pollutant levels. After multi-pollutant adjustment, the increase in risk was most prominent after four to five days in diabetic patients. The risk of CRAO onset also significantly increased in patients with hypertension and

in patients ≥65 years old after just one day of elevated pollutant levels. The results demonstrated a positive association between air pollution and CRAO onset, particularly in patients with diabetes or hypertension and those older than 65 years.

Ophthalmology 2016;123:2603-2609
Cheng HC, Pan RH, Yeh HJ, Lai KR, Yen MY

Intravitreal Bevacizumab for DME

Researchers from the U.K. wrote that since outcomes of intravitreal anti-vascular endothelial growth factor injections are variable among individuals with diabetic macular edema, they set out to determine the ocular and systemic predictors of DME response to intravitreal bevacizumab. The study was a retrospective review over two years. They defined an anatomical response to IVB as a 20-percent reduction in central macula thickness after the first course (three injections) of IVB.

Long-term visual acuity changes in DME weren't significantly different between eyes with and without systemic hypertension

In 78 eyes of 54 individuals, 28 percent of cases had an anatomical response after the first course of IVB. Systemic hypertension (odds ratio: 12.1; 95 percent-CI: 0.7 to 21) was a statistically significant predictor (p=0.025) of a good response to IVB, while previous macular laser was a statistically significant (p=0.0005) predictor of a poor response (odds ratio: 0.07; 95-percent CI: 0.01 to 0.32). Sixty-eight percent of eyes underwent subsequent treatment for DME after the first course of IVB. The visual acuity gain at 24 months in hypertensive individuals (0.7 ±3.6 letters) and nonhypertensive individuals (5.2 ±3.7 letters) was not statistically significantly different (p=0.41). Researchers concluded that hypertension was a positive predictor, and previous macular laser was a negative predictor of response to IVB. However, they found that long-term visual acuity changes weren't significantly different between eyes with or without systemic hypertension.

Clin Ophthalmol 2016;10:2093-8
Joshi L, Bar A, Tomkins-Netzer O, et al.

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Sunday, February 19
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After participating in this educational activity, attendees should be able to:

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- Engage in discussions related to emerging issues in glaucoma, including risk assessment, imaging, management and progression assessment
- Manage glaucoma using newer treatments available: surgical and pharmaceutical
- Discuss the newest glaucoma surgical devices, including those used in patients undergoing cataract surgery
- Describe outflow biology and its relevance to MIGS while citing relevant MIGS studies and trials
- Utilize advanced technologies and techniques in refractive cataract surgery, including advanced technology IOLs
- Outline current management and treatment of dry eye and keratitis.
- Discuss the rationale for anti-VEGF therapy and steroids in posterior segment diseases including age-related macular degeneration and diabetic macular edema
- Managing IOP in retina disease state treatments
- Navigate issues relating to patient compliance/adherence with eye drop medications
- Describe how various imaging technologies, such as OCT and angiography, can assist in diagnosing and monitoring ocular conditions
- Discuss options for cosmetic skin procedures

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A 10-year-old boy presents at Wills for help with long-standing blurry vision in one eye.

Jordan D. Deaner, MD, and Carol L. Shields, MD

Presentation

A 10-year-old African-American boy presented for further evaluation of blurred vision in his left eye that persisted over the past five years. His decreased visual acuity (20/20 OD, 20/200 OS) was first noted on a routine school vision screening at age 5; however, his parents were not informed of the vision problem at that time. Later, at age 8, the child was diagnosed with amblyopia on ophthalmic examination and he was instructed to begin patching his right eye. Initially the visual acuity improved, but it subsequently regressed, following admittedly poor compliance with patching by the parents. The child continued intermittent patching, but two years later demonstrated a left esotropia. He had been evaluated by three different ophthalmologists before coming to Wills. The first two ophthalmologists found no organic cause for the amblyopia and encouraged patching. The third physician identified an inferior retinal detachment and referred the child to an ocular oncology center for further evaluation. *(The differential diagnosis for retinal detachment in pediatric cases appears in Table 1, below.)*

Table 1. Diagnosis of Pediatric Detachment

The differential diagnosis of retinal detachment in a child includes congenital, inflammatory, traumatic, neoplastic and degenerative conditions. The most important conditions include:

- Inflammatory
  - posterior uveitis
  - posterior scleritis
- Traumatic
  - blunt trauma/foreign body retinal detachment
  - abusive head trauma with retinal detachment
  - retinal dialysis
- Neoplastic
  - retinoblastoma
  - retinal hemangioblastoma
  - choroidal hemangioma
  - choroidal melanoma
  - choroidal nevus
- Vascular/degenerative vitreoretinopathy
  - Coats disease
  - familial exudative vitreoretinopathy
  - retinopathy of prematurity
  - juvenile X-linked retinoschisis
  - rhegmatogenous retinal detachment
  - traction retinal detachment
  - Stickler's syndrome

Medical History

The patient had no additional prior ocular history. His birth history was only notable for a faint red birthmark on the left upper eyelid that spontaneously resolved during his first few years of life. Past medical history revealed an isolated episode of altered mental status at the age of 2. Medical evaluation at that time demonstrated normal brain magnetic resonance imaging and electroencephalogram. He also had a history of asthma and seasonal allergies. Family history was noncontributory and there were no known drug allergies. His medications included albuterol, cetirizine and nasal fluticasone.

Examination

Ocular examination demonstrated visual acuity of 20/20 OD and 20/400 OS (pinhole to 20/200). Pupils were equal, round and reactive to light, with no relative afferent pupillary defect. Extraocular eye movements were full bilaterally. The

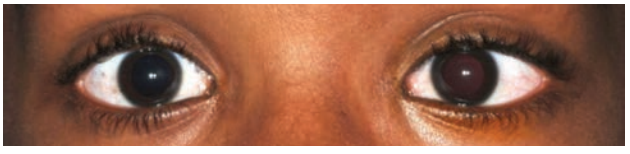

Figure 1. External photograph demonstrating left esotropia by Hirschberg corneal reflex and the absence of cutaneous nevus flammeus. Fundus examination of the right eye was normal. The left eye revealed an inferior retinal detachment with a red-orange hue to the entire fundus, suspicious for a solid choroidal mass (Figure 2).

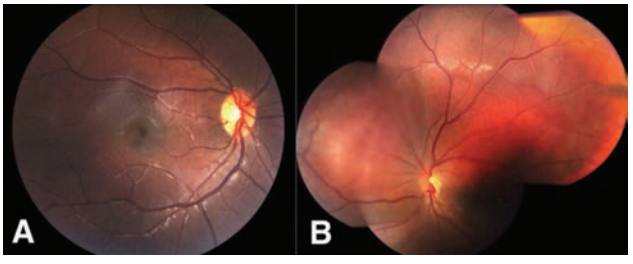

Figure 2. Fundus photograph of (A) the normal right eye and (B) affected left eye demonstrating a diffuse red-orange choroidal mass with associated inferior retinal detachment, suggestive of diffuse choroidal hemangioma.

patient demonstrated 20 prism diopters of left esotropia in primary gaze. Applanation tonometry revealed intraocular pressures of 10 mmHg in each eye. External examination was normal without birthmark or nevus flammeus *(Figure 1)*. Slit lamp exam demonstrated few conjunctival papillae and mild constitutional melanosis, bilaterally.

What is your differential diagnosis? What further workup would you pursue?

Diagnosis and Workup

"Tomato catsup fundus" is a term often used to describe the red-orange choroid seen in patients with diffuse choroidal hemangiomas. The patient's left fundus was suspicious for this *(Figure 2)* and further diagnostic testing was pursued. B-scan ultrasonography confirmed an inferior retinal detachment and demonstrated a solid echodense choroidal mass of 5.3 mm in maximum thickness, consistent with a diffuse choroidal hemangioma *(Figure 3)*. Optical coherence tomography also demonstrated choroid thickening, and overlying subretinal fluid was noted with no view of the foveola *(Figure 4)*.

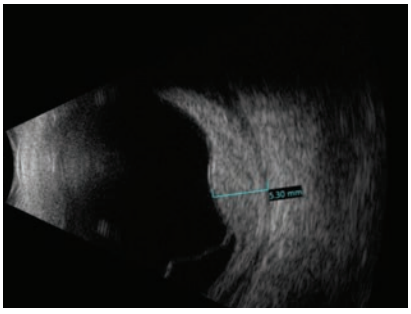

Figure 3. B-scan ultrasound demonstrating an inferior retinal detachment and a solid echodense choroidal mass measuring 5.3 mm in maximum thickness.

With the addition of the findings on B-scan and OCT, a final diagnosis of diffuse choroidal hemangioma was made. Options for management included external beam radiotherapy, proton beam radiotherapy, plaque radiotherapy and photodynamic therapy. Given his young age and the concern for external radiation exposure, localized plaque radiotherapy was performed.

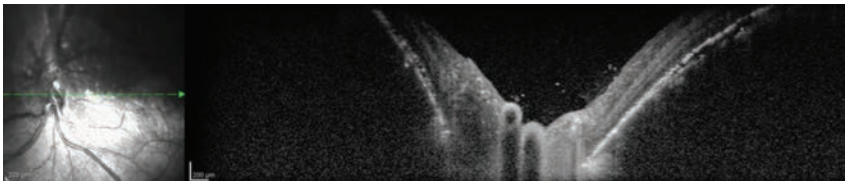

Figure 4. OCT of the papillomacular region shows the optic nerve centrally and massive choroidal thickening surrounding both sides of the disc and elevating the retina. There was no view of the foveola.

Treatment

The patient was treated with Iodine-125 plaque radiotherapy. The plaque was positioned directly over the mass posteriorly with transcleral radiation delivery to an apex dose of 35 Gray. To achieve this dose, the plaque was sutured in place for four days. Topical antibiotic/corticosteroid ointment and atropine ophthalmic drops were used for three weeks. At five months follow-up, the tumor had regressed and the subretinal fluid was completely resolved *(Figure 5)*. By ultrasonography, the hemangioma regressed from 5.3 to 3 mm in thickness *(Figure 6)*. The macula was flat on OCT, but there were residual subfoveal RPE changes *(Figure 7)*. Visual acuity remained stable at 20/20 OD and 20/200 OS.

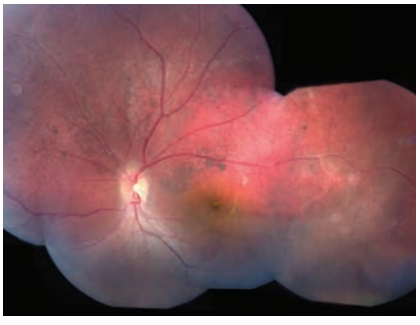

Figure 5. Fundus photograph of the left eye showing tumor regression, resolution of subretinal fluid and residual RPE changes.

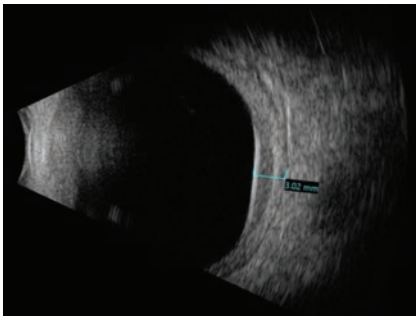

Figure 6. Postoperative B-scan ultrasonography demonstrating resolution of the retinal detachment and regression of the choroidal mass to 3 mm in maximum thickness.

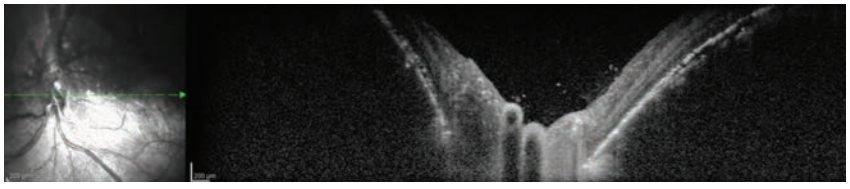

Figure 7. Postoperative OCT of the macula demonstrating resolution of the retinal detachment, a flat fovea and residual RPE changes.

Discussion

Choroidal hemangioma is a benign vascular hamartoma that can be separated into two subtypes: circumscribed and diffuse.[1] The etiology of vision loss in choroidal hemangioma can be attributed to foveal distortion, subretinal fluid, intraretinal edema, induced hyperopia, amblyopia or a combination of these factors.[2] Diffuse choroidal hemangioma appears clinically as a diffuse, red-orange thickening of the posterior choroid, displaying the appearance of the aforementioned "tomato catsup fundus."[1]

The diagnosis of diffuse choroidal hemangioma is often made on clinical fundus examination with indirect ophthalmoscopy, with ancillary testing generally used for confirmation. In cases complicated by secondary total retinal detachment, clinical examination may be limited, so characteristic features of ancillary testing play an important role.[3] B-scan ultrasonography demonstrates an echodense dome-shaped mass, often with subretinal fluid.[4] On A-scan ultrasonography the mass may demonstrate high internal reflectivity.[4] Fluorescein angiography shows diffuse lesion hyperfluorescence in the pre-arterial phase and can be useful in determining the exact site of leakage in large tumors.[4] Indocyanine green angiography demonstrates rapid filling of the mass by one minute with washout by 10 to 15 minutes, often with a ring of staining.[5]

Once the diagnosis of diffuse choroidal hemangioma is made, this should prompt a systemic evaluation for the neuro-oculocutaneous Sturge-Weber Syndrome. Choroidal hemangioma can be present in up to 55 percent of cases.[6] The diagnosis of Sturge-Weber Syndrome is established clinically with the presence of a cutaneous capillary malformation (nevus flammeus) in combination with a vascular anomaly of the brain (leptomeningeal hemangiomatosis), best seen on brain MRI.[7,8] Associated features include seizures (80 percent),[9] focal neurologic deficits (65 percent)[9,10] and mental retardation (60 percent).[10] The frequency and severity of seizures and neurologic deficits are related to the location and extent of associated capillary venous malformations. Seizure control can be achieved with anti-epileptic medications or surgery if the seizures prove to be refractory to medical management.[11]

Additional ocular manifestations of Sturge-Weber Syndrome include glaucoma (30 to 70 percent) as well as capillary venous malformations of the episclera or conjunctiva (69 percent).[12] The cause of glaucoma associated with Sturge-Weber Syndrome is not fully understood and the age of onset may inform the mechanism. In younger children it may be the result of anterior chamber angle anomalies, while in older children it is thought to result from elevated episcleral pressure.[12] Nonetheless, glaucoma in these individuals is notoriously difficult to control. Medical therapy is typically only a temporizing agent and surgical correction with goniotomy, trabeculotomy or a glaucoma drainage device is often necessary in these cases.[13]

The management of diffuse choroidal hemangioma depends on the extent of the patient's visual compromise, association with subretinal fluid, and lesion size. Asymptomatic diffuse choroidal hemangiomas can be observed by monitoring for subretinal fluid biannually.[4] If the patient is symptomatic, treatment options include photodynamic therapy, external beam radiation therapy, plaque radiotherapy and propranolol.

Laser photocoagulation has been used in the past, with some efficacy for the treatment of circumscribed choroidal hemangiomas. In one study, 62 percent of patients had resolution of subretinal fluid and 71 percent had stable or improved VA.[14] However, subretinal fluid limits the therapeutic efficacy of laser therapy and therefore may not be a reasonable treatment option in patients with large diffuse choroidal hemangiomas associated with extensive subretinal fluid. In these patients, treatment with external beam radiotherapy or plaque radiotherapy has been most effective. The primary complications of laser photocoagulation can include RPE atrophy, scotoma and epiretinal membrane formation.[14]

Photodynamic therapy, like laser photocoagulation, is advantageous as it avoids radiation exposure. Photodynamic therapy also spares the retina and retinal vasculature, compared to other forms of therapy. Also, like laser photocoagulation, it has proven effective in the treatment of circumscribed choroidal hemangioma, with 100 percent of patients achieving resolution of subretinal fluid in one study.[15] On the other hand, photodynamic therapy has had limited success in treatment of diffuse choroidal hemangioma, resulting in mixed outcomes, with one case report demonstrating resolution of subretinal fluid and tumor regression after a single treatment[16] and another requiring multiple repeat treatments.[17]

External beam radiation therapy has been used with lens-sparing doses, resulting in good outcomes. Resolution of subretinal fluid occurred in 100 percent of patients in a small study (n=15), tumor regression occurred in five patients, and visual acuity improved in seven. Shortcomings of EBRT include radiation exposure and the need for patient cooperation

during treatments.[18]

Propranolol has also been used with mixed results. While two case studies have shown that oral propranolol can be used effectively in the treatment of exudative retinal detachment secondary to diffuse choroidal hemangioma,[19,20] another has demonstrated its failure.[21] Propranolol generally fails to induce tumor regression despite the fact that it might resolve subretinal fluid.

Plaque radiotherapy is an important treatment option, particularly for patients with extensive subretinal fluid. In a retrospective review of five patients, plaque radiotherapy demonstrated efficacy in both subretinal fluid resolution (100 percent) as well as tumor regression (100 percent) at the 32-month follow-up.[22] Visual acuity was stable or improved in four out of the five patients.[22] Plaque radiotherapy is advantageous given its application of precise, localized therapy for a short duration (four days), and minimal reliance on patient cooperation.[22] We elected plaque radiotherapy for our patient given his young age and our desire to limit the patient's radiation exposure.[22]

In the case presented here, the boy had been unsuccessfully treated for amblyopia for five years. His treatment failure, initially attributed to noncompliance, was later found to be the result of a serous retinal detachment secondary to a diffuse choroidal hemangioma. Our patient was successfully treated with plaque radiotherapy and ultimately showed subretinal fluid resolution, hemangioma regression and stable visual acuity.

This case underscores the importance of a thorough examination to evaluate the patient for all possible organic causes of amblyopia prior to assuming that lack of progress or visual regression is due to patient non-compliance with treatment. REVIEW

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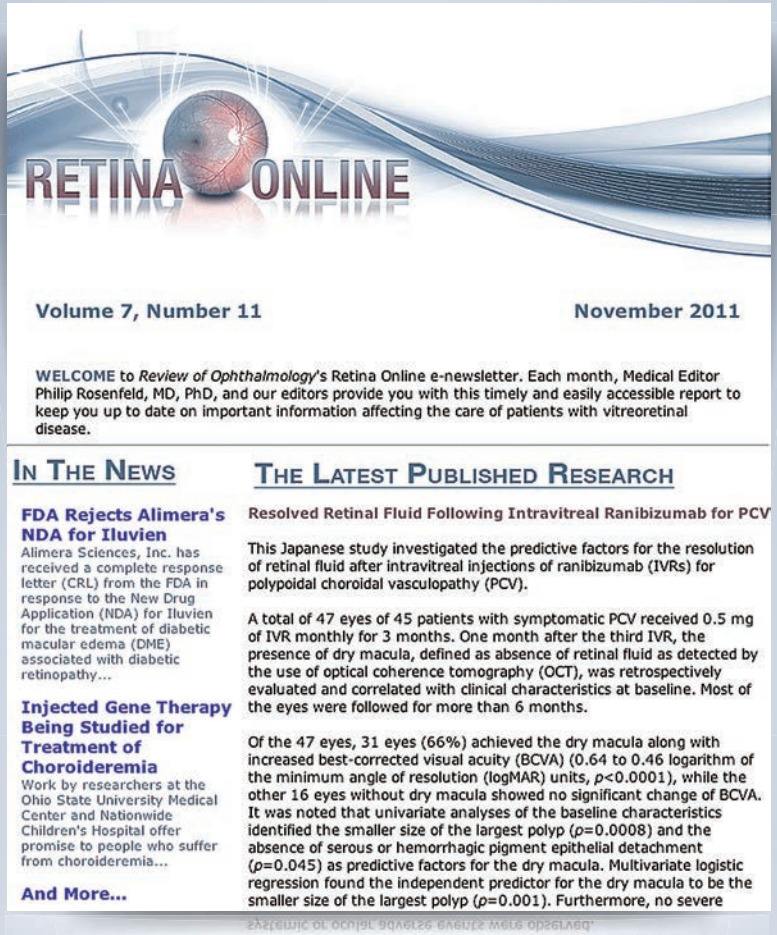

RETINA ONLINE

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A total of 47 eyes of 45 patients with symptomatic PCV received 0.5 mg of IVR monthly for 3 months. One month after the third IVR, the presence of dry macula, defined as absence of retinal fluid as detected by the use of optical coherence tomography (OCT), was retrospectively evaluated and correlated with clinical characteristics at baseline. Most of the eyes were followed for more than 6 months.

Of the 47 eyes, 31 eyes (66%) achieved the dry macula along with increased best-corrected visual acuity (BCVA) (0.64 to 0.46 logarithm of the minimum angle of resolution (logMAR) units, $p<0.0001$), while the other 16 eyes without dry macula showed no significant change of BCVA. It was noted that univariate analyses of the baseline characteristics identified the smaller size of the largest polyp ($p=0.0008$) and the absence of serous or hemorrhagic pigment epithelial detachment ($p=0.045$) as predictive factors for the dry macula. Multivariate logistic regression found the independent predictor for the dry macula to be the smaller size of the largest polyp ($p=0.001$). Furthermore, no severe

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