REVIEW® of Ophthalmology

May 2017

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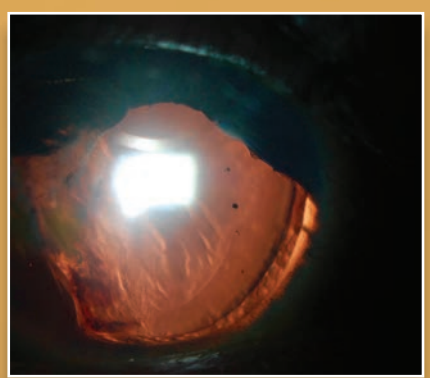
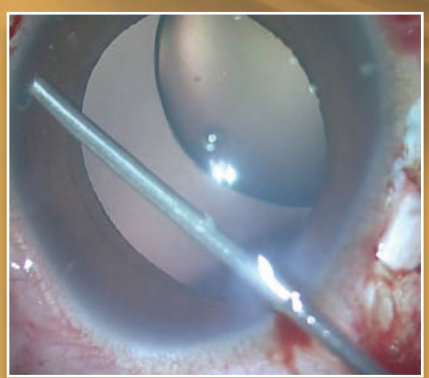
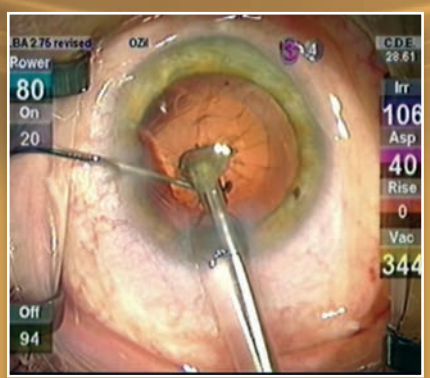
How to Get A Cataract Procedure Back On Course







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REVIEW NEWS
Volume XXIV • No. 5 • May 2017

Physicians Warn of The Perils Of "Stem Cell Therapy"

A recent study published in the *New England Journal of Medicine* reviewed the negative consequences of bilateral ocular injections of purported stem cells received by three women at a clinic in south Florida in 2015.[1] All three women suffered major vision loss, associated with ocular hypertension, hemorrhagic retinopathy, vitreous hemorrhage, combined traction and rhegmatogenous retinal detachment or lens dislocation; one participant ended up with no light perception.

The clinic offering this treatment was listed as participating in a clinical trial of the intravitreal injection of stem cells derived from autologous adipose tissue as a treatment for non-neovascular macular degeneration. The trial was listed on clinicaltrials.gov, even though it had no investigational new drug application with the FDA. The patients undergoing the procedure had seen the study listed on that website and assumed they were participating in the clinical trial. (The trial itself was withdrawn in September, 2015, before enrollment had actually begun.) The written information given to the patients did not mention any association with a clinical trial, or approval by an institutional review board. All three patients paid $5,000 out of pocket for the procedure.

According to the authors of the *NEJM* study, subcutaneous adipose tissue was taken from each patient and processed to isolate the putative stem cells. The resulting cells were suspended in a solution of platelet-rich plasma created from the individual's blood; the mixture was injected intravitreally in both eyes on the same day. Patients were instructed to use one drop of topical moxifloxacin three times a day for three days after the injection.

> *"[The patients] seemed to think at some point they were [in a trial], but there was no evidence in the paperwork they showed us that they did participate in a trial."*
> *— Thomas Albini, MD*

Within a week, all three of the individuals had presented to other vision clinics (two of them to the Bascom Palmer Eye Institute) suffering loss of vision and other symptoms. Despite extensive treatment and surgery over a period of months, all three suffered debilitating vision loss: One was left with perception of hand motion in one eye and light perception in the other; one was left with 20/200 vision in one eye and perception of hand motion in the other; and the third ended up with no light perception in either eye.

"What makes this type of procedure so risky is the lack of any preclinical (animal) or clinical trial data on the procedure," says Thomas Albini, MD, an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute at Miami, and co-author of the *NEJM* paper. "It's never been properly studied. It seems that clinics have succeeded to some degree in treating patients with joint disease using intra-articular injections; they may have assumed it would be safe to inject into the eye in a similar fashion, but the risk of complications appears to be much higher in the eye."

Dr. Albini notes that clinicaltrials.gov is overseen by The National Institutes of Health, not the U.S. Food and Drug Administration. "The site was intended to serve as an all-inclusive repository of clinical trials, with a low bar for the inclusion of any particular trial," he says. "It was not designed to evaluate or approve any of the clinical trials in any way. I think the legislation that created the site didn't foresee that it could be used as a type of advertising for these clinical procedures.

"When we met the patients, we weren't sure whether they were in a trial or not," he continues. "They seemed to think at some point that they were, but there was no evidence in the paperwork they showed us that they did participate in a trial."

Philip Rosenfeld, MD, PhD, a professor of ophthalmology at the Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine,

(Continued on page 7)

Ophthalmic Product Development Insights

Matthew Chapin & Malcolm Ngiam

Recognizing Additional Value in China

There's tremendous interest in ophthalmology from companies around the globe, as well as a wide range of ophthalmic deal structures that demonstrate the creativity that biotech and pharma partners can bring to bear when securing the rights for new pipeline products. In the last installment of Ophthalmic Product Development Insights, we highlighted some general elements related to early product development in Japan, and approaches to regulatory discussions that may be useful to the entrepreneur investigating ex-U.S. strategies for partnering and funding. This month we shift our attention to China, and how focusing on such an emerging market—and possibly securing a deal with a regional company—can add significant value.

China has a population of more than 1.3 billion people, many of whom have cataracts. A growing number of individuals in China also have chronic conditions such as retinal disease, glaucoma and dry eye, and the ophthalmic business tracking firm Market Scope projects that the Chinese ophthalmology market will approximately double by 2021, from $2.7 billion to $5.3 billion. China is certainly an important emerging market and can play a key early role in a product-development program.

Here are some examples of how one might approach an opportunity in China, depending on the stage of development at which a company finds itself:

• *Early-stage projects trying to bridge a funding gap to move forward into the investigational new drug application (IND) stage, and clinical proof-of-concept in the United States.* Engaging with a partner in China in a deal in which that company could secure early regional rights, an early option or license fee could help supplement other financing or, in some cases, maybe secure enough funding to move its project to the next step in the United States.

• *After a value inflection in the United States (such as Phase II), either before or during engagement with other pharmaceutical partners for licensing/acquisition.* In this instance, discussion with Asian partners can add a complementary strategy for showing a deal's momentum, or may even be the exit point in a situation in which the Asian partner may seek global rights itself.

• *In discussions with a global pharmaceutical company.* In this case, you may want to hold back and carve out a specific region such as China. Since the Chinese market is still emerging, keeping rights to China while you license your product to the rest of the world may not affect the deal value as it would if you were to hold back major markets such as Europe or Japan. Holding back China and collaborating with a regional company based in Asia might allow you to focus on strategies for bringing your product to market sooner than you otherwise could.

Or, in some cases, a global pharma company may not have plans to enter China in the foreseeable future; therefore additional value will be left on the table if you don't pursue a deal with a regional player in China.

With these potential strategies in mind, it's important for the new entrepreneur/startup CEO to understand the potential value that a deal with a regional Chinese company may hold, and to consider when/if timing may be appropriate to consider such an approach. Some high quality regional companies in China are also becoming more aggressive and focused on bringing in products from the United States, and thus are open to creative deals for investing in new projects.

Next, we'll review a specific example of a regional company in China that collaborated with a global pharmaceutical company.

The company is called Essex Bio-Technology, and is based in Hong Kong. Essex has extensive experience in ophthalmology, and sells its own growth-factor product in China for use in dry eye, ocular trauma and post-refractive surgery healing. Notably, Essex is also Pfizer's exclusive importer and distributor of Xalatan and Xalacom in China (which had already been approved in China before Pfizer's relationship with Essex). Essex has an extensive reach into China's ophthalmology network, with 1,280 sales reps. By working with Pfizer, Essex has benefited intangibly on corporate governance and strategic planning. The two companies have established a long-term, symbiotic relationship through a sharing of resources, and appear to have successfully tackled China's challenging market.

Essex is also in the process of pursuing a development program in the United States for its growth-factor formulation for anterior segment disease, for which it will ultimately be seeking a U.S. partner. In the future, Essex hopes to expand into therapies for the posterior segment, as well as for wound healing, oncology and neurodegenerative disease.

Other Considerations

As China's population grows wealthier and older, the health-care industry will need to focus on primary care through improved primary screening methods to better manage chronic diseases. Diagnostic tests with higher sensitivity and specificity will allow for better patient care through personalized medicine.

Historically, the process for bringing a drug that's in late-stage development or that's already approved in the United States into the Chinese market has been a laborious process that has taken years, and has generally required repeating studies either in China or in a Chinese population. Therefore, having late-stage clinical data from outside China has been a key to driving a program into China.

In order to navigate the regulatory pathway, communication with China's version of the Food and Drug Administration, the CFDA, is critical. CFDA as an organization is evolving to ensure that its structure, processes and policies are in line with the exponential growth of the health-care industry domestically and internationally. CFDA has in place similar mechanisms akin to an FDA pre-IND meeting, and embraces face-to-face meetings as well, with an appointment made well in advance. While CFDA has a fair system which allows foreign companies to request meetings, it may still be beneficial for foreign companies to engage relevant local partners

(Continued on page 6)

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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; 2016.

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REVIEW® of Ophthalmology

(Continued from page 4)

for better engagement on such matters, since these partners may be more savvy regarding local culture and formalities.

Recent guidance from China's FDA suggests that it's striving to help companies be more efficient when bringing novel products into China, and this may lead to some altered requirements, such as with the need to repeat safety or other early trials in China, or relying on development in the United States to occur first. Strategies are situational and, in some cases, U.S. or global data may not be necessary, and product development can begin in China. This progressive approach represents CFDA's advancing policies and its recognition that it needs to bring innovative products to China.

The CFDA has put forth many interesting policies that may enhance China's competitiveness on the world stage. These policies include its approach to multicenter clinical trials in which investigative sites in China may be part of a global or U.S.-based program, and the CFDA's stated intention to speed up early-stage clinical trials of foreign drugs without late-stage trials having taken place elsewhere. This forward-looking approach will help accelerate China's position within the health-care industry. In ophthalmology, retina diagnostics and treatment are areas of high interest, given the demographics of China's population.

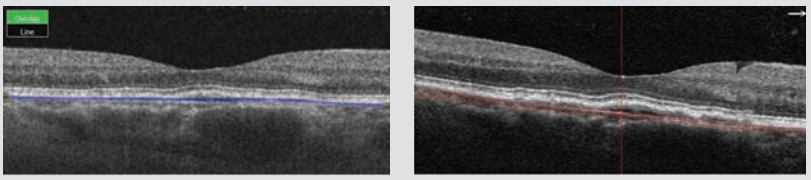
Another consideration is price expectations. While China may present itself as a large economy, suggesting good potential commercial returns, the reality of China's demographics shows significant wealth disparity with varying levels of purchasing power within the country. With this in mind, China is doing its best (through various policies) to ensure wide affordability for health care. State regulation on pricing (as part of its Universal Health Care coverage) is one method that is commonly applied through a tender system, taking into consideration many parameters (i.e., epidemiology of diseases, product indication, volume of sales, frequency of prescription and usage, etc.). Under newer policies, the health-care industry is expected to self-regulate to ensure competitive prices, underpinned by state-regulated revision of prices (which may be revised dramatically). Amid the expectation of affordable health care for all, it would be important for the entrepreneur to take into consideration tiered (i.e., decreasing) royalties based on sales and pricing levels when negotiating a license deal in China. Understanding a potential regional partner's position and the reason for these tiered royalties during a negotiation will help ensure a mutually successful deal.

We hope this brief review has highlighted the opportunities of this region, and demonstrated how a relationship with a regional player can become part of a strategy for an early-stage program seeking creative ways to move forward.

Mr. Chapin is Senior Vice President of Corporate Development at Ora. Ora provides a comprehensive range of development, clinical-regulatory and product consulting services for developers, investors and buyers; preclinical and turnkey clinical trial services; assistance with regulatory submissions; and the integration of business development and financing support in ophthalmology. Mr. Ngiam is deputy general manager (Business Development) at Essex Bio-Technology. We welcome your product development comments or questions. Please send correspondence to mchapin@oraclinical.com or visit oraclinical.com.

Correction

In the April 2017 installment of Retinal Insider, the SS and SD OCT-B scans at the bottom of Figure 1 were reversed. The correct image and corresponding caption appear below.



Choroidal neovascularization at the level of the choriocapillaris. The image on the left was imaged on the Topcon DRI Triton device. The image on the right was imaged on the OptoVue RTVue XR Avanti.

(Continued from page 4)

and a co-author of the *NEJM* paper, notes that paying for the procedures should have been a red flag. "No reputable clinical trial would charge them for this procedure," he says. "This type of procedure is experimental—there's no proven benefit from stem cell transplantation into the eye for any retinal disease."

Asked why this wasn't against the law, Dr. Albini notes that many companies and patients believe that stem cell therapies need to be brought to market as quickly as possible. "That's probably the reason that government agencies like the FDA haven't pushed for further restriction on these clinics," he says. "The FDA has clarified multiple times over the past five years that these clinics need to get FDA approval for this type of procedure, but they haven't followed that with legal action directed at clinics that are clearly in violation of that clarification. It will be interesting to see whether these few cases will push the needle towards more government intervention."

Dr. Albini notes that there are things a clinician can do to help prevent future problems. "Always insist that intravitreal injections be performed by an ophthalmologist, as suggested by the American Academy of Ophthalmology, or even better, by a retina specialist with experience in treating retinal disease," he says. "Let your patients know that stem cell clinics often lack the ophthalmic expertise required to perform these procedures, and that even if a clinic does have that expertise—i.e., an ophthalmologist is performing the injection—the procedure has never been studied rigorously and the patient is consequently taking a huge risk. There's no evidence that the methods used by any clinic result in better vision. On the other hand, we know for sure that these procedures can result in blindness." REVIEW

1. Kuriyan AE, Albini TA, Townsend JH, et al. Vision loss after intravitreal injection of autologous "stem cells" for macular degeneration. N Engl J Med 2017;376:1047-53.

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Down, Boy.

Help Tame Postoperative Ocular Inflammation and Pain With LOTEMAX® GEL

Indication

LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information about LOTEMAX® GEL

- LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, and where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Patients should not wear contact lenses when using LOTEMAX® GEL.
- The most common ocular adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

Please see brief summary of Prescribing Information on adjacent page.

LOTEMAX® GEL
loteprednol etabonate
ophthalmic gel 0.5%

BAUSCH + LOMB

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Lotemax Gel safely and effectively. See full prescribing information for Lotemax Gel.

Lotemax (loteprednol etabonate ophthalmic gel) 0.5%

Rx only
Initial Rx Approval: 1998

INDICATIONS AND USAGE

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops.

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections

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

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

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

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when LOTEMAX is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

US Patent No. 5,800,807

LGX.0114.USA.16

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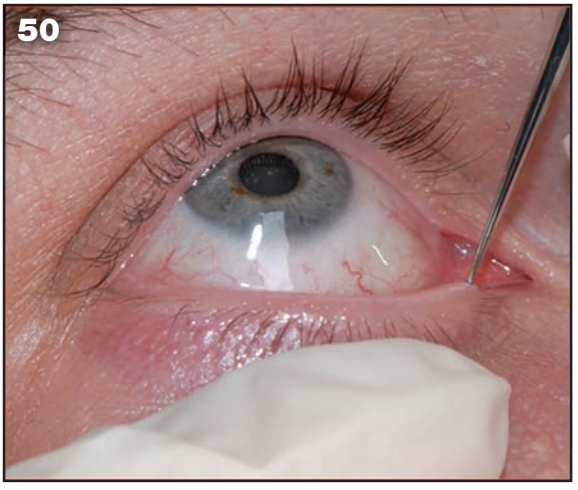

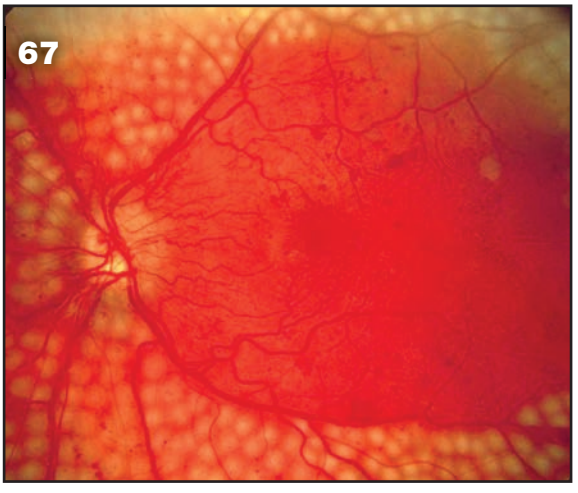

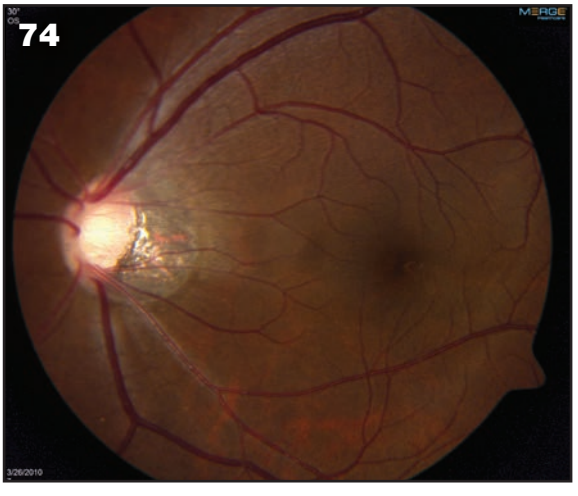

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EDITORIAL STAFF

Editor in Chief
Walter C. Bethke
(610) 492-1024
wbethke@jobson.com

Senior Editor
Christopher Kent
(814) 861-5559
ckent@jobson.com

Senior Associate Editor
Kristine Brennan
(610) 492-1008
kbrennan@jobson.com

Associate Editor
Liam Jordan
(610) 492-1025
ljordan@jobson.com

Chief Medical Editor
Mark H. Blecher, MD

Art Director
Jared Araujo
(610) 492-1032
jaraujo@jobson.com

Senior Graphic Designer
Matt Egger
(610) 492-1029
megger@jobson.com

International coordinator, Japan
Mitz Kaminuma
Reviewophthalmo@aol.com

Business Offices
11 Campus Boulevard, Suite 100
Newtown Square, PA 19073
(610) 492-1000
Fax: (610) 492-1039

Subscription inquiries:
United States — (877) 529-1746
Outside U.S. — (845) 267-3065
E-mail:
revophthalmology@cambeywest.com
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REVIEW Editor's Page

Walter C. Bethke, Editor in Chief

Hard to Miss, Easy to Ignore

Recently, a relative of mine woke up on a Monday with body aches and a fever. Oddly, and to add just a little more discomfort, the palms of her hands were red. "They feel like I got a rope burn playing tug-of-war," she told her husband, then flopped back into bed.

When a day of rest and fluids didn't do anything but allow the fever to climb near 103 degrees amid some bouts of diarrhea, they managed to get a last-minute appointment with a nurse practitioner at a specialist's office. Now, the woman was dizzy and a little lightheaded, symptoms which were chalked up to the towering fever. A physical exam led the NP to believe the woman was fighting some kind of infection, not yeast infection or a urinary tract infection as she first thought, but something. The possibility of the flu was brought up, as was, God forbid, toxic shock syndrome, though the NP discounted the latter because the woman didn't have the usual predisposing factors. She knew the patient had an appointment with her family physician that afternoon, so they asked her to make sure he ruled out the flu.

At the general practitioner's, there was a lot more head scratching as my relative detailed her symptoms—the aches, fever, dizziness, diarrhea and the odd, burnt-feeling hands. The doctor dismissed the flu since the patient had no respiratory issues at all, and he also didn't give much weight to the other physician's suggestion of toxic shock. Most of the symptoms were consistent with an infection that most likely would respond to antibiotics, he explained. "As for the hands thing, that's just weird. I don't know what that's about," he said, and sent the patient on her way.

Fast-forward 24 hours. After three doses of the drugs, the only positive was that the fever had come down by 1 degree. Everything else was in plague overdrive: vomiting; diarrhea; and body aches so bad she could barely move. She couldn't open pill bottles with her hands—the "rope burn" had become too painful. A call to the family doctor was met with incredulity. "Go to the hospital? Why? You've only been on antibiotics for a day!" But she and her husband both knew something was wrong. Worst-case-scenario wrong. A five-second Internet search for toxic shock syndrome and there it was, four bullet points down in the list of symptoms: "A rash resembling a sunburn, particularly on the palms and soles of the feet." An hour later, she was being treated for toxic shock syndrome at the hospital, and hopes to make a full recovery in a month.

And this brings me to this month's issue. The surgeons we spoke to for features on cataract complications say that, like those odd "burnt" palms, similar subtle, anomalous signs can occur during surgery, too: a small bounce of the chamber or a little tilt to the nucleus. Rather than noticing these signs but forging onward in the belief (hope?) that it's still just a routine case, experts say it pays to take them seriously. Stop. Investigate. Give these signs their due. Doing so might just save the patient's vision.

—Walt Bethke, Editor in Chief

Discover Strength in efficacy

As demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in patients with DME

Choose EYLEA® (aflibercept) Injection from the start

Learn about EYLEA at EYLEA.us/ro

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

REGENERON

06/2016
US-LEA-1648(1)

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR) in Patients with DME. The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

2.7 Injection Procedure. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (*see Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA.

Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (*see Adverse Reactions*). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (*see Dosage and Administration and Patient Counseling Information*).

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (*see Adverse Reactions*). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular edothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (*see Dosage and Administration*).

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

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

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

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

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

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

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

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

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

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

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

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

- Hypersensitivity including rash, pruritus, and urticaria as well as isolated cases of severe anaphylactic/anaphylactoid reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

8.3 Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (*see Warnings and Precautions*). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (*see Adverse Reactions*). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

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Making the Cut: Capsulotomy Devices

Achieving a strong, centered, perfectly circular capsulotomy may soon become simpler and easier.

Kristine Brennan, Senior Associate Editor

A right-size, centered and circular capsulotomy is arguably the most important part of refractive cataract surgery. Capsulorhexis has evolved from an exit incision for the crystalline lens into the foundation of good IOL position and the good visual outcome that accompanies it. Femtosecond laser-assisted surgery has made capsulotomy more precise—but only for those practices that are able to afford and accommodate a femto system. Accordingly, manual capsulorhexis remains the prevailing technique. It is difficult to master, however.

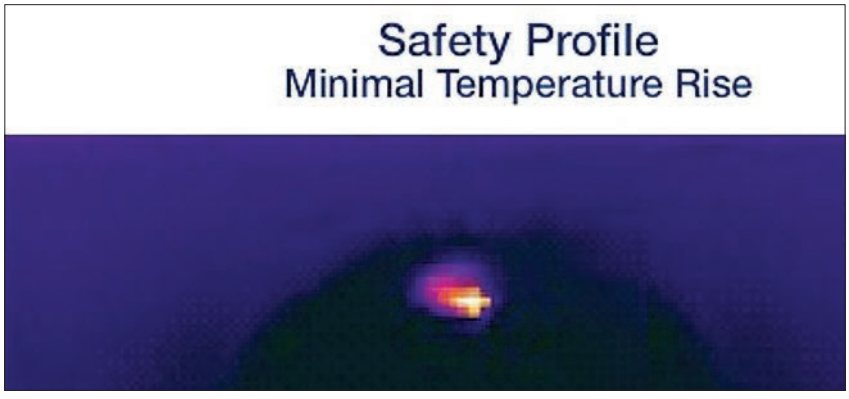
This state of affairs has been the status quo since the advent of femto in 2008, leaving room for the emergence of devices that promise to assist in the safe, fast creation of consistently strong and circular capsulotomies with less expense than that associated with femtosecond lasers.

Here are three products in development that aim to fill that void.

CAPSULaser

The CAPSULaser (CAPSULaser; Los Gatos, Calif.), the only laser in the group, relies on continuous thermal energy to create capsulotomies. After dilating the pupil and making side-port incisions, the surgeon stains the anterior capsule with trypan blue to visualize the CAPSULaser's anatomical target. The CAPSULaser, which can be adjusted to select diameters from 4.5 to 7 mm, projects a pattern for the surgeon to follow with the laser. Unlike femto, this laser is continuous rather than pulsed. In one three-second pass, it creates a circular capsulotomy.

Richard Packard, MD, FRCS, FRCOphth, Prince Charles Eye Unit, King Edward VII Hospital, Windsor, England, notes that besides being fast and elegant, a CAPSULaser capsulotomy may be stronger and more elastic than those made by CCC or by femtosecond laser because its energy denatures the collagen. "In the region of irradiation, the laser energy facilitates the molecular phase change of the capsular collagen IV to elastic amorphous collagen. As the collagen undergoes this phase change it creates the capsulotomy with a rim that has a high degree of elasticity and tear strength associated with the amorphous collagen," he explains. Dr. Packard adds that this



Richard Packard, MD, FRCS, FROphth

IR image of capsulotomy being performed with CAPSULaser. The manufacturer says that a peak temperature of 67°C (white zone) is reached for an instant during the procedure.

strengthens the capsulotomy, potentially stabilizing the anterior capsule, which in turn can provide more consistent effective lens positioning.

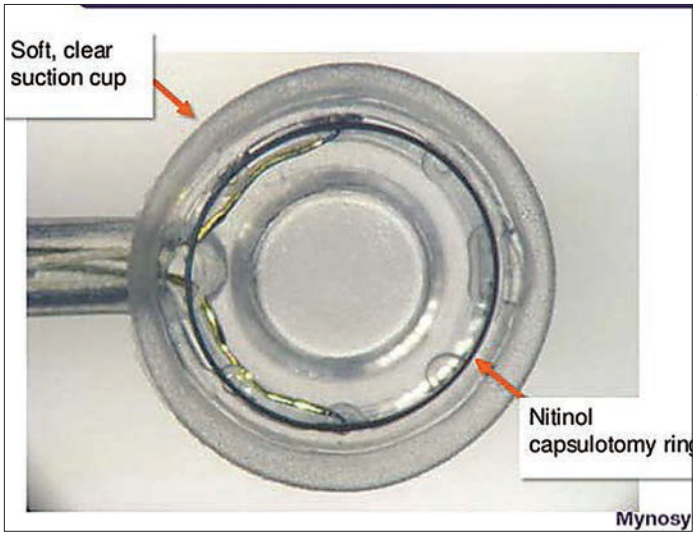
CAPSULaser has completed preclinical testing on porcine and human cadaver eyes; Dr. Packard's investigation of the device's ability to make free-floating, centered and circular capsulotomies has been encouraging. Since the CAPSULaser uses low levels of continuous energy to make capsulotomies, the device momentarily raises the temperature of the the iris, corneal endothelium and retina by less than 0.2°C as measured by infrared imaging and thermocouple.

The CAPSULaser attaches to a standard surgical microscope, so its maker says it's easily transportable and its use doesn't require moving the patient to another location for the capsulotomy.

Zepto

The Zepto (Mynosys Cellular Devices; Fremont, Calif.) uses a method called "precision pulse capsulotomy." The non-laser device consists of a console with a disposable handpiece equipped with a flexible nitinol ring designed to cut a capsulotomy cap about 5.2 mm in diameter. The ring folds to enter incisions as small as 2.2 to 2.4 mm, then springs back into shape. A suction cup placed over the capsular membrane pulls it gently towards the ring, which cuts a cap in 3.69 seconds with minimal disruption to the zonules. The user then discards the disposable cutting element on the tip of the handpiece, along with the removed capsular membrane slice.

Mark Kontos, MD, a senior partner at Empire Eye Physicians, which has offices in eastern Washington and northern Idaho, has a femto system but appreciates the simplicity and flexibility of the Zepto. During his time on Mynosys's medical advisory board, Dr. Kontos had the opportunity to use the device in a laboratory setting. "Using the Zepto takes all of a couple of seconds," he says. "You insert the device, center it on the lens, press the foot pedal and it all happens in seconds. It's very quick and very easy, and it really doesn't require any kind of new skill set from a cataract surgeon's point of view: You're just inserting another device inside the eye and the learning curve is extremely short."



Mark Kontos, MD

The Zepto's disposable cutting element includes a suction cup that gently draws the membrane towards the nitinol wire ring.

Dr. Kontos also notes that surgeons can adapt their use of the Zepto as the case demands. "You can center it however you decide to—or decenter it as you want to. Let's say that you have a patient who has a high angle kappa or something like that; if for some reason, you decide you want to center the capsulorhexis slightly nasal, you can. It gives you the flexibility of putting it more or less wherever you want," he says.

The Zepto console is small, and the device doesn't need to be attached to a microscope head, so it can potentially blend in with a practice's established flow.

Mynosys says that the Zepto can produce consistently circular capsulotomies not attainable with manual CCC, and it doesn't require a clear cornea. "You could put it into an eye with a cornea that has very poor visibility and still be able to get a perfect capsule out of it," says Dr. Kontos. He adds that the Zepto can make a successful capsulotomy in poorly dilated pupils more easily than a laser can. "The pupil will come down, and sometimes it will come down to the point where it's very difficult to do a laser treatment. With the Zepto, you can slide it underneath the iris, so you can still make a perfectly round, centered capsulotomy even if you don't have a widely dilated pupil. It doesn't damage the iris in any way."

The Zepto produces maximum temperature increases in the eye of no more than 2.01°C, according to Mynosys. The precision pulse capsulotomy method employed by the Zepto created smooth, flexible capsulotomy edges with tear strength exceeding that of edges made by manual CCC and femtosecond laser in one U.S. study of cadaver eyes partially sponsored by Mynosys.[1]

Mynosys is currently seeking a 510(k) clearance from the FDA, and the Zepto is currently in use abroad.

ApertureCTC

This device's maker, International BioMedical Devices (Charleston, S.C.), says the "CTC" stands for "continuous thermal capsulotomy,"

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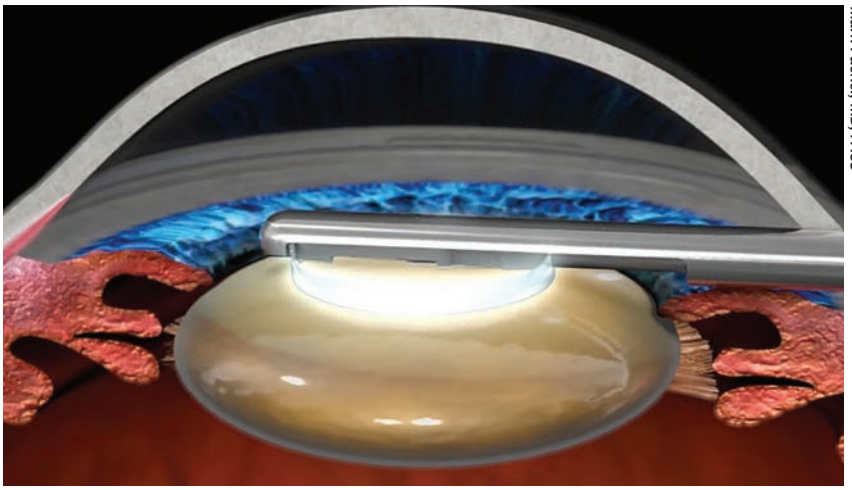

Mark Packer, MD, FACS

An illustration of the ApertureCTC's thermal element in contact with the caspsule. The disposable ring provides continuous, all-points contact with the membrane to cut a uniformly smooth and circular capsulotomy. The rings are available in a range of diameters.

which allows uniform contact with the anterior capsule. The manufacturer adds that the ApertureCTC can cut a capsulotomy rapidly, with repeatable circularity and centration. The device consists of a console that provides constant, safe, low-level energy to the cutting parts of the capsulotomy tip of the handpiece, which is designed to look and feel like one used in phaco.

The ApertureCTC handpiece is used with disposable steel rings ranging from 4.5 to 6.5 mm in diameter. In use, the ring attaches to the tip of the 1.2-mm handpiece and retracts at the sides to fit through a small incision. Once over the anterior capsule, the user expands the ring back out to its original shape. The ring delivers thermal energy to the capsular membrane and captures the circular cap for removal. Because it relies on thermal energy, and all points of the ring are in contact with the membrane at all times during the capsulotomy, Mark Packer, MD, FACS, says the procedure can be completed in milliseconds under the protection of an OVD. "As the ring is retrieved, it automatically captures and removes the perfectly circular cap," notes Dr. Packer, who is chief medical officer for IBMD. "The disposable tip is discarded after the case, and the reusable handpiece is sterilized in standard fashion.

"The key features of the ApertureCTC are its continuous 360° thermal element, which overcomes the inevitable gap required by radiofrequency devices with loop-wire or ring cutting elements; and its uniform contact with the anterior capsule, which obviates the necessity for vacuum suction," he continues. "This technology has the potential to ensure safer cataract surgeries and may also provide more predictable visual outcomes for patients.

"We are currently in preclinical-stage testing," says Dr. Packer of the device's ongoing development. REVIEW

Dr. Packard is a consultant and equity shareholder in CAPSULaser. Dr. Kontos reports no relevant financial interests. Dr. Packer is the chief medical officer of International BioMedical Devices, Inc.

1. Thompson VM, Berdahl JP, Solano JM, Chang DF. Comparison of manual, femtosecond laser, and precision pulse capsulotomy edge tear strength in paired human cadaver eyes. Ophthalmology 2016 Feb;123:2:265-74.

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Anterior Segment Tech: A Screening Primer

Christopher Kent, Senior Editor

Surgeons offer tips for making the most of the latest anterior segment measuring devices.

Every refractive surgeon knows that screening patients is an important way to avoid unhappy outcomes (and the lawsuits that may accompany them). However, as anterior segment technology advances and new instruments appear, the best ways to accomplish that continue to change. Here, three surgeons well-versed in the latest technologies offer their advice on how to make the most of current screening options.

Going Beyond Topography

There's no question that topography is still the mainstay when it comes to screening. "Careful screening of refractive surgical patients for the risk of postoperative ectasia continues to be important in clinical practice," says Stephen D. Klyce, PhD, adjunct professor of ophthalmology at Mt. Sinai University School of Medicine in New York City. "Trained use of Placido topography remains the most reliable and sensitive method for detecting the earliest changes associated with keratoconus. With the emphasis placed on proper fixed, standard scales and contrasting color palettes to avoid interpretation errors, nearly all corneas with early signs of keratoconus can be detected."[1]

At the same time, there's been a proliferation of new instruments that can provide relevant information. "In recent years, anterior segment imaging has evolved significantly," says A. John Kanellopoulos, MD, clinical professor of ophthalmology at NYU Medical School in New York and medical director of the Laservision.gr Institute in Athens, Greece. "Today it involves several technologies besides traditional topography and tomography. We currently use a large number of other anterior segment imaging devices, including anterior segment OCT and the HD Analyzer—the latter being an optical scatter measuring device—to better evaluate the tear film and the clarity of both the cornea and the intraocular lens.

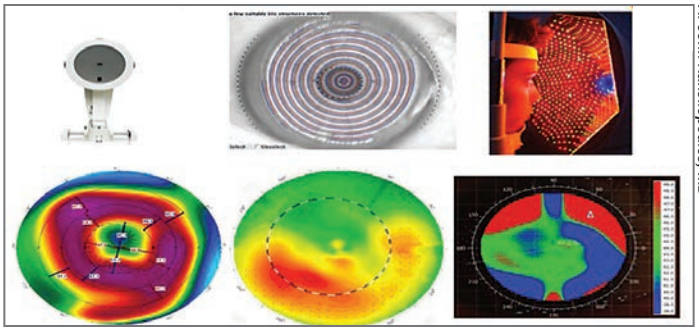
"Each anterior segment imaging device has advantages and disadvantages," he continues. "Classic Placido disc topography doesn't provide any data regarding corneal thickness or posterior corneal curvature, but it gives us good anterior curvature maps. It's very accurate in an eye that has a good tear film, even if the cornea has opacities. Corneal tomography, which evolved from the original Orbscan to today's Pentacam and other Scheimpflug devices, can produce pachymetry maps of the cornea, showing the anterior and posterior elevations. This technology gives us a three-dimen-

This article has no commercial sponsorship.

sional diagnostic modality, allowing earlier diagnosis of ectasias and significant corneal irregularities. It can also calculate total corneal power, which is normally in the 43- to 45-D range. However, these instruments depend on corneal clarity, so any disruption of clarity will cause them to work suboptimally.

"The new kid on the block is the multicolor LED-reflection topography device called Cassini," he continues. "Cassini does ray-tracing on every three of 700 spots that are projected onto the cornea, imaged and then analyzed. Notably, this provides good central cornea data; Placido disc imaging doesn't give us any central cornea data because curvature calculation starts from the first Placido disc, not from the center. The Cassini also offers some posterior curvature data to use as a second data source to compare with Pentacam data or data from other types of anterior segment imaging."

Dr. Kanellopoulos notes that many of these devices have their own software, programmed to help the clinician detect irregularities. "Our group has reported what may be the largest evaluation of the different parameters associated with keratoconus, in a study using these technologies to evaluate more than 1,000 keratoconic eyes," he says. "We found that the 'index of height decentration,' a corneal symmetry index available in the Pentacam and many other topography devices, is probably the most sensitive tool for diagnosing early ectasia and ectasia progression—with the exception of very centrally located cones. Also very helpful for diagnosing early ectasia is a well-known software program created by Belin and Ambrosio that evaluates the qualitative transition of corneal pachymetry, found on the Pentacam. In the final analysis, however, the surgeon's eye and experience may be the best way to detect irregular corneal pachymetry map patterns, no matter how sensitive these software programs are."



A. John Kanellopoulos, MD

It's important to consider how each technology gathers its information when interpreting the result. This patient had a simple case of central cloudy dystrophy (Francois). The Pentacam (left), which uses Scheimpflug cross-sections of the cornea to generate its topographic map, is affected by the cloudiness and shows a significant central depression that's not really there. In contrast, both Placido and Cassini's reflection-based technologies are able to make accurate measurements.

Working With the Technology

The following strategies can help ensure that problematic eyes don't end up undergoing surgery:

• ***Don't screen patients without using a tomographic analysis.*** "Today I think it's generally accepted that patients need to be screened with a tomographic device—in other words, an instrument that can analyze more than just the front surface of the cornea," says Michael W. Belin, MD, professor of ophthalmology and vision science at the University of Arizona in Tucson. (Dr. Belin, working with Renato Ambrosio, MD, developed the Belin/Ambrosio Enhanced Ectasia Display—sometimes called the BAD display—which was incorporated into the Oculus Pentacam and is now one of the most commonly used refractive surgery screening tools.) "Without that capability, you're conducting less than half an exam," he says.

At the same time …

• ***Don't rely solely on tomographic data.*** Dr. Klyce points out that four different technologies can currently be used to obtain topographic information. "Several new instruments sport both Placido and slit-scan capabilities," he says. "They have the potential to provide accurate corneal topography, pachymetry and endothelial elevation data. In terms of topographic representation, listing them from most sensitive and faithful to least, they are: grid-style reflection topographers; traditional Placido disk topographers; very high resolution swept-source OCT; and corneal curvature derived from slit-scan elevation measurements."

Dr. Klyce notes that abnormal corneal topography is the highest risk factor for the development of ectasia following refractive surgery,[2] so proper interpretation of corneal topography is important. "While risk factors have been found to include corneas less than 510 µm thick, a residual stromal bed less than 250 µm, being less than 26 years of age and myopic corrections greater than -8 diopters, it's been proven that recognition of corneal abnormality in topography outweighs the other risk factors," he says. "Recently there's been a trend toward using non-Placido slit-scan tomographers alone to assess the corneal status. That trend is understandable because helpful adjunct information such as accurate corneal thickness profiles—and for the cataract surgeon, endothelial astigmatism—can be derived using this modality. However, it's clear that when low-sensitivity corneal tomography exams are used rather than reflection-based corneal topography, experts' ability to recognize abnormal topography is challenged."[3]

• ***Consider using an all-in-one instrument that can obtain multiple kinds of data.*** "When performing refractive surgery, a good reflection topographer and a good tomographer are essential, and these capabilities can be combined into a single instrument," says Dr. Klyce. "For the refractive cataract surgeon, it's ideal to use an instrument that can perform good reflection topography; has slit-scanning capabilities to measure corneal pachymetry, endothelial astigmatism and anterior chamber depth; and can measure axial length. Recently, all-in-one instruments that can provide all of these data in one platform have been introduced. In addition, for the clinical scientist, some instruments now available can also measure phakic and pseudophakic intraocular lens tip, tilt and centration. With careful evaluation for accuracy, the all-in-one instruments are especially attractive for their efficiency in terms of exam time and instrument space requirements."

• ***Remember that OCT is the most accurate way to measure corneal thickness.*** "We've published reports comparing tomographic and OCT measurements of corneal thickness," says Dr. Kanellopoulos. "Comparing them side-by-side, OCT is far more accurate. It's only a matter of time before most spectral-domain OCTs will have an anterior segment option available, which will enable clinicians not only to use this technology for very accurate macula and retina imaging, but also for very accurate anterior segment diagnosis and treatment."

• ***Keep in mind how each instrument is generating the data it gives you.*** "It's important to understand how each technology generates its map," Dr. Kanellopoulos points out. "Different instruments may produce a very different map of the same eye. If you understand what each device is doing, you can interpret the scan appropriately. For example, the patient in the figure on p. 23 has Central Cloudy Dystrophy of Francois, causing a benign clouding of the central cornea. The Pentacam scan, which uses Scheimpflug cross-sections of the cornea to generate its map, is biased by the cloudiness and shows a significant central depression that's not really there. However, both Placido and Cassini topography are able to make accurate measurements."

• ***Because measurements made with different technologies may not agree, remember that your experience with a given technology matters.*** "Accurate gold standards are available for reflection corneal topography," says Dr. Klyce. "However, once data is derived from images or signals passing through the eye, assumptions must be made regarding the index of refraction along the pathway of the probing beam or ray. A good example of this uncertainty is the average central corneal thickness measured with ultrasound—approximately 560 µm—vs. the average CCT measured with confocal microscopy or slit-lamp pachymeters, which is approximately 520 µm. That's a 40-µm difference. The bottom line is that clinical experience with a specific instrument is necessary in order to obtain reliable results. So, when updating or converting to a newer technology, be careful to ensure that the new data are equivalent to the old. If they're not equivalent, be sure that conversion tables are available."

• ***Consider imaging the corneal epithelium with OCT.*** "Imaging the corneal epithelium with anterior segment OCT is easy and clinically useful," notes Dr. Kanellopoulos. "Our group has reported on this extensively. We believe that doing this is pivotal, not just for refractive surgeons but for ophthalmologists in general. The corneal epithelium appears to be very uniform in most healthy patients of any age, sex and refractive error, so any deviation from uniformity in the corneal epithelium points to ocular disease, whether it's dry eye, early keratoconus, trauma, blepharitis or some other disturbance.

"Up until recently, imaging the corneal epithelium wasn't practical for an everyday ophthalmology office," he continues. "Now, anterior segment OCT can provide brilliant topographic maps of both the total cornea and the corneal epithelium, in a point-and-shoot fashion. This can help the clinician establish homogeneity and good conditions before prescribing even spectacles. It can also help us make more advanced diagnoses to follow up a diagnosis of dry eye. Furthermore, it can help us make an early keratoconus diagnosis—even before topography is altered—because the epithelium tends to mask the earliest changes in corneal stromal thickness, and this allows us to detect that *(see example, p. 26).*

"In general, anterior segment OCT is a very useful tool for following refractive surgery patients," he adds. "It can reveal a lot about how transient dry eye affects quality of vision, as well as the progress that occurs following any interventions the ophthalmic surgeon decides to make."

• ***Remember to consider the age of the patient.*** "We all know that age is an important factor in determining whether or not someone is an appropriate refractive surgery candidate," says Dr. Belin. "If someone is 55 years old, we're willing to accept a lot more leeway in some of our measurements than if the patient is 19. Up to now, the BAD test has not accounted for this factor, so surgeons had to remember to account for the patient's age when deciding whether to proceed. An age-adjusted display is something we'd like to incorporate into the next version of the test."

• ***High asymmetry between the eyes is a red flag.*** "This should always be a sign to proceed with caution," notes Dr. Belin. "To use an analogy, if patients come into your office with intraocular pressures of 12 mmHg in

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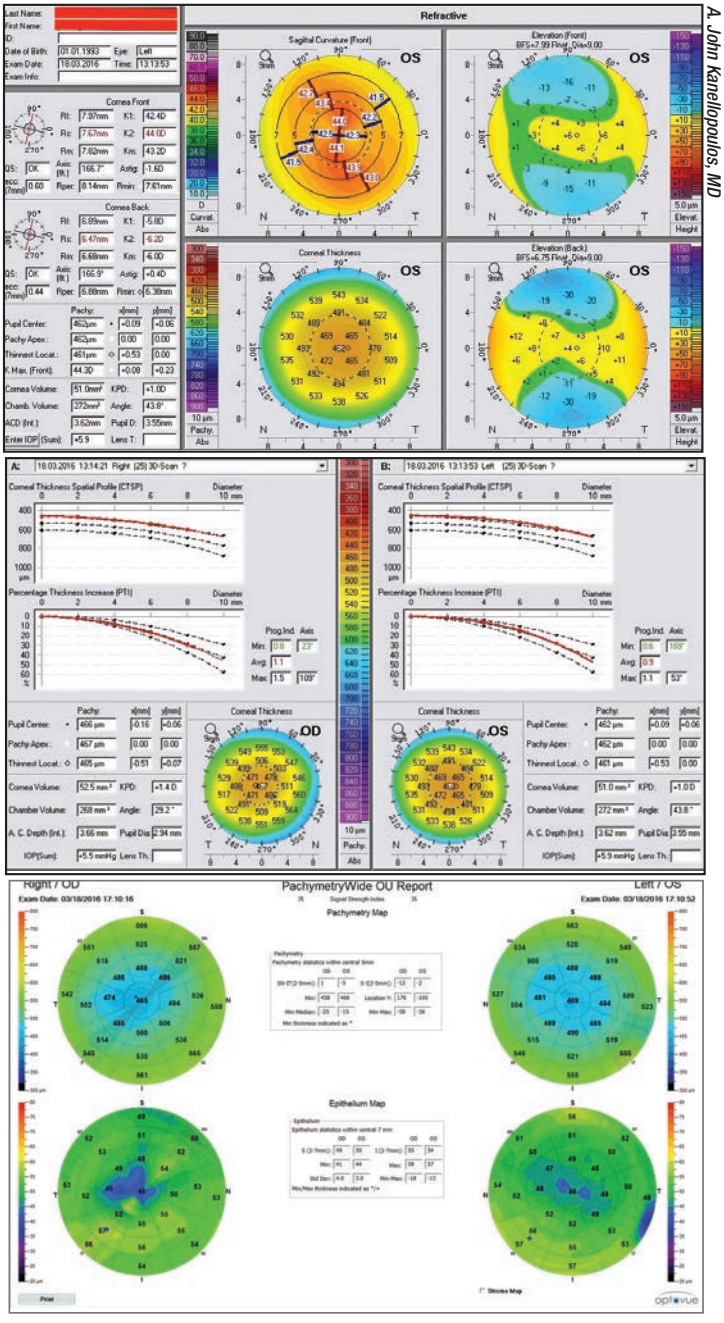
both eyes, or even 19 mmHg in both eyes, you probably wouldn't be concerned. But if they had pressures of 12 in one eye and 19 in the other, you'd probably want to follow them. It's true for most things in medicine: Asymmetry is a red flag."

• ***Keep in mind that dry eyes can cause bogus tomographic and OCT readings.*** "Surgeons often overestimate corneal thickness and the irregularity of posterior corneal curvature in tomographic maps and OCT scans when the patient has dry-eye syndrome," says Dr. Kanellopoulos. "A dry eye creates epithelial injury and significantly skews the Scheimpflug imaging. Thus it's very common to have irregular Pentacam and OCT pachymetry maps that do not accurately represent the true pachymetry in dry eyes."

• ***Don't depend too much on screening tests.*** "This may seem strange, given that I've developed a number of screening tests, but the biggest mistake I think surgeons make is becoming too dependent on the displays," says Dr. Belin. "The displays are there to assist the physician, not to replace the physician. You need to look at a number of other factors when evaluating a patient, including age, family history, ablation depth and the amount of correction needed. The display is there to assist your decision-making process, but it shouldn't have the final say."



Imaging the corneal epithelium may reveal important details relevant to screening and treatment decisions. This 22-year-old male had 20/20 vision OU, but had a brother with keratoconus. A Pentacam scan shows only regular, thin corneas, but OCT epithelial maps confirm keratoconus (thinning over the cone), hidden by epithelial remodeling.

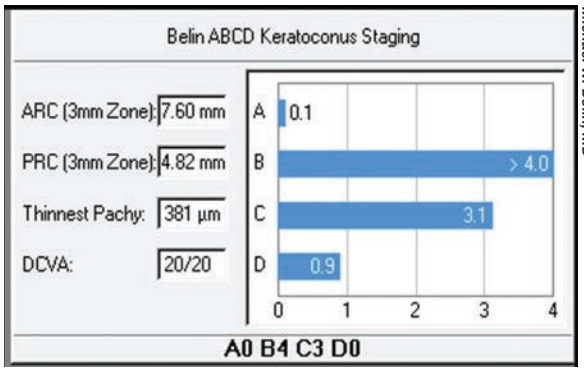
Screening: The Next Level

With the advent of collagen cross-linking availability in the United States, American doctors' ability to treat ectasia and keratoconus has taken a giant leap forward. That, in turn, has made it important to be able to go beyond simply determining that an abnormality is present—the goal of basic screening—to being able to determine exactly what is wrong and whether the process is progressive. "Cross-linking has been available for more than a decade outside the United States, and we see two common but opposite problems: too many people with nonprogressive disease being treated who probably do not require treatment, and too few who have progressive subclinical disease receiving treatment early enough to prevent loss of visual quality," says Dr. Belin.

"About a year and a half ago Dr. Ambrosio and I participated in the Global Consensus on Keratoconus and Ectatic Diseases project, which invited ophthalmic experts from around the world to reach a consensus about the definition and management of keratoconus and ectatic disease," he says. "That work resulted in an article published in *Cornea* last year.[4] One of the major conclusions of the consensus document was that we still don't have an adequate way of classifying or staging ectatic disease. That's become a particularly

A. John Kanellopoulos, MD

important issue with the advent of collagen cross-linking. So, for the past two years we've been working on this, and about six months ago we released a new classification system that we call the ABCD system, currently available on the OCULUS Pentacam. *(See illustration, right.)* It can be incorporated into any tomographic system that's able to measure both the anterior and posterior surfaces."



Michael W. Belin, MD

The new Belin ABCD Keratoconus Staging Display allows the clinician to describe the cornea's condition based on four measurements, graded 0 to 4. Above: A typical patient with advanced subclinical disease. The anterior surface is normal (A0), while the posterior surface has a marked ectatic change (B4) accompanied by moderately advanced corneal thinning (C3). Because the anterior surface is normal, the distance visual acuity is good (D0).

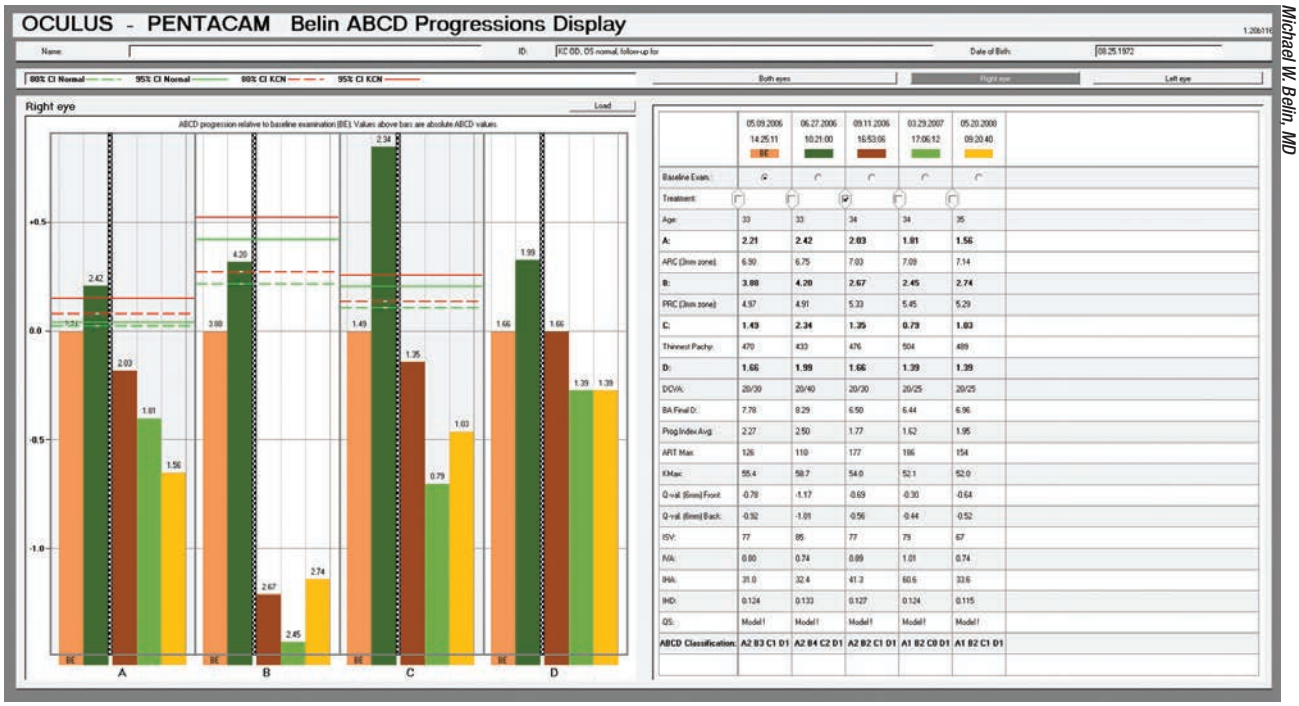
Dr. Belin notes that most ophthalmologists continue to use the Amsler-Krumeich classification system to stage ectatic disease. "That was first described about 70 years ago, yet people still refer to it in published papers," he points out. "It uses a parameter called K-max to determine when and if progression has occurred. The problem with K-max is that it's an anterior-cornea parameter. That means that in order to detect progression, the anterior surface must have changed, so by the time you detect progression the patient has already lost visual acuity. Our goal should be to prevent the loss of vision, not to halt a decrease that's already occurring. To do that, we need to be able to identify progressive disease at a much earlier stage.

"Compare this to oncology," he continues. "Oncologists classify disease today based on a very detailed staging mechanism: whether you have nodes; whether you have hormone receptors; the extent of the disease; whether it's contiguous or noncontiguous; and other factors. The system we continue to use to stage ectatic disease is based on data from a keratometer and an optical pachymeter. And we wonder why we can't come up with a good description of how we treat this disease."

Describing the Disease

Dr. Belin explains that in the ABCD classification system, each anatomical part of the cornea is individually described. " 'A' stands for the anterior radius of curvature, taken from a 3-mm zone centered on the thinnest point on the cornea," he says. " 'B' stands for the back of the cornea, meaning the posterior radius of curvature, also based on the 3-mm optical zone that's centered on the thinnest point. 'C' stands for corneal thickness at the thinnest point. (In contrast, the Amsler-Krumeich system uses the central corneal thickness.) 'D' stands for distance visual acuity. The ABCD system allows you to describe each factor independently, graded from 0 to 4."

Dr. Belin says that part of the challenge of creating the ABCD test was determining the inherent noise level of the four parameters. "We did that using two different patient populations: a known keratoconic population and a normal population," he says. "The reason we used two populations is that a keratoconic population inherently has more noise in the measurements.



Michael W. Belin, MD

The new Belin ABCD Progression Display may make it easier to monitor the progression of ectatic disease over time. This display shows five exams, two prior to cross-linking and three after treatment. In this patient, it reveals statistically significant progression on both the anterior and posterior corneal surfaces, as well as progressive thinning; it documents significant improvement post-cross-linking. In addition to the graphic display, the table shows how a number of other commonly used parameters have changed.

If you want to determine whether a 47-year-old with keratoconus is undergoing progressive change, for example, you'd probably want to compare him to a keratoconic population. But if your patient is a 15-year-old who has a very early or subclinical disease, his cornea will behave more like those in the normal population. The tolerance level for the latter patient is much smaller.

"Our ultimate goal was to create a progression display that allows you to track change over time and document improvement after treatment such as cross-linking," he continues. "The new Belin ABCD Progression Display allows you to graphically display both an 80 and 95 percent confidence interval, for both a normal and a keratoconic population. *(See example, above.)* That will allow you to determine when and if true, statistically significant change has occurred. The goal of this, again, is to be able to identify very early disease, finding changes in either corneal thickness or the posterior surface before loss of vision has occurred. That should allow us to treat patients early enough to prevent vision loss, while avoiding unnecessary treatment in older patients with static disease."

How BAD Works With ABCD

Dr. Belin says the ABCD classification and staging system and the BAD display are somewhat different but complementary. "The BAD test is designed to separate normal from abnormal patients," he explains. "It gives you a number that tells you how far from normal the patient is, but it doesn't describe the condition of the disease or help you determine where and when progression is occurring.

"To use an analogy, the BAD display is like the 'check engine' light in your car," he says. "It tells you that something is wrong, but it doesn't tell you what the problem is. The ABCD displays are more geared toward analysis of the problem. So, for example, if someone comes to see me for refractive surgery, my first concern is: Are you an appropriate candidate or not? If the BAD test indicates that the person is abnormal, then I won't do refractive surgery. Nevertheless, that individual needs further evaluation to determine exactly why the eye is abnormal, and more important, whether the abnormality is progressive.

"I wouldn't pursue that in the refractive part of my practice, partly for practical reasons and partly because of insurance, but I would have that individual examined in the medical portion of my practice," he continues. "That's the point at which the ABCD classification system and the progression display would be most useful. It will provide information relevant to proceeding with cross-linking, refractive surgery, intracorneal rings or DALK, because just as with breast

cancer, we need to be able to stage the disease to properly determine what the treatment should be.

"To illustrate the importance of this for a surgeon who performs combined cross-linking and refractive surgery," he continues, "suppose your patient has an advanced case of posterior ectasia. He might be an appropriate candidate for cross-linking, but you wouldn't want to combine refractive surgery and cross-linking because the anterior surface is normal. And of course, the ABCD system can be used thereafter to monitor progression; the BAD test cannot."

Dr. Belin says many patients could potentially benefit from this. "Patients who have very early-stage disease that hasn't affected their vision yet won't normally seek medical care, because they're asymptomatic," he points out. "However, they often seek refractive surgery, where hopefully they will be screened as abnormal. As more refractive surgeons offer cross-linking to their patients, all of these tests should be of great use to them." Dr. Belin says the new ABCD progression display should be available this spring.

The Evolution Continues

Dr. Klyce notes that, despite the potential for conflicting data from the various technologies, the incidence of postoperative ectasia is low and may be declining. "The combination of appropriate color maps that display corneal curvature and interpretive software programs trained to recognize different corneal abnormalities has helped clinicians to differentiate between normal topography and variations that signal abnormalities," he says.

"Meanwhile, modalities other than topography and pachymetry for detecting at-risk corneas are also under active investigation," he continues. "Reinstein and collaborators have shown that patterns characteristic of keratoconus can be observed in corneal epithelial profiles using very high frequency ultrasound.[5] Since ectasia is the consequence of a biomechanical failure of the corneal stroma, it's heartening that corneal biomechanics are being extensively studied. New keratoconus-detection algorithms have been developed combining corneal biomechanical response data with corneal tomographic data, leading to excellent discrimination.[6] Using a materials-science approach to model the viscoelastic properties of the corneal stroma, researchers have been able to predict specific corneal shape changes in individual corneas with known risk factors.[7]

"Whether this approach will ever be sensitive enough to detect the very early structural weakening that underlies the subtle curvature changes detected with topography remains to be seen," he adds. "However, when instruments provide accurate data from both imaging technology and biomechanical measures, these data can be combined to develop expert systems whose aim is to recognize corneal risk with a greater predictive value than can be obtained from a single type of measure." REVIEW

Dr. Belin is a consultant to Oculus, but receives no compensation for sales of instruments using his displays. Dr. Klyce is a consultant for Nidek. Dr. Kanellopoulos is a consultant for Avedro and Alcon.

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How to Handle Eyes With Unstable Zonules

Jeffrey S. Eisenberg, Contributing Editor

Cataract surgery in these cases becomes much more difficult, but not impossible.

If you've ever been on a trampoline, you were able to bounce safely because the springs that connect the fabric to the frame kept it taut. Now imagine that some or all of those springs are damaged and you jump: The result won't be good.

The zonules holding the capsular bag in the eye function similarly, and when they're weak or missing during surgery, complications result.

Zonular instability is no doubt the bane of many a cataract surgeon, as the risk for the cataract moving posteriorly or the vitreous moving anteriorly becomes higher, putting patients at risk for such complications as a retinal hole or detachment. In this article, expert surgeons share their best techniques for managing these cases.

Early Clues

Though you won't often know the patient has weak zonules until you're performing the procedure, you may see some clues during your preop exam. In particular, look for:

• ***History.*** Patients who are likely to have zonular weakness include those who have severe pseudoexfoliation with severe phacodonesis, high amounts of myopia, a history of trauma, Marfan's syndrome, homocystinuria and retinitis pigmentosa."You need to be ready to deal with that in the operating room," says Brandon Ayres, MD, of Wills Eye Hospital in Philadelphia.

Also, you should let these patients know beforehand that their cataract procedures may be more complex. "On one side, we don't want to scare patients because they typically have great outcomes," says Brad Feldman, MD, of Wills Eye Hospital. "But I think it's important to let them know about this condition."

One additional note: When you do see a patient with loose zonules, it's important to understand the etiology. "Sometimes there may not be an obvious reason," says Mike Snyder, MD, of the Cincinnati Eye Institute. "Consider, though, that patients with undiagnosed Marfan's syndrome or homocystinuria are at risk for aortic aneurysm and coronary artery disease, respectively. That's why patients with loose zonules should be referred for a cardiac ultrasound or bloodwork and an echocardiogram."

• ***Slit lamp exam.*** Look for phacodonesis by having the patient in several directions and watch for lens movement. Dr. Feldman will repeatedly tap the slit lamp table with his fist to look for subtle lens instability (after warning the patient, of course). "Some-

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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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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.

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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 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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times we'll actually see the cataract jiggle. Sometimes we see shallowing of anterior chamber or the cataract tilted up against the iris," he says. "Besides that, in cases where the patient is well-dilated, we may see areas where zonules are absent or are stretched."

Iris defects should serve as a red flag, as well. "Whenever I see iris damage or a section of the iris that's been modified, iridodialysis or something of that nature in the area where the iris is damaged, the support system may have been damaged," Dr. Ayres says.

• ***Biometry.*** A deep anterior chamber also suggests possible risk. "The support system may already be weak, allowing the lens to sit farther back in the eye," notes Dr. Ayres. "In that instance, vitreous gel may already be entering the anterior chamber."

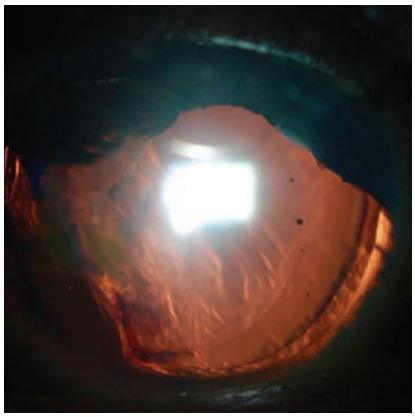
• ***Dilation.*** Keep in mind that the pupils of patients with pseudoexfoliation, Marfan's or some other systemic conditions often don't dilate fully.

Emergency Preparedness

Though you may see clues to zonular weakness during your preop workup, it's more likely that you'll see them during the actual cataract procedure. "With most patients, the presence and degree of zonular instability is a surprise that reveals itself during surgery," Dr. Feldman says.

So, surgeons say you should prepare your OR in advance. Specifically, you'll want to have capsule support hooks, a capsular tension ring, triamcinolone (to visualize vitreous gel), and a vitrector on hand. "This is your emergency kit," Dr. Ayres says. "This is what you want to have close access to."

You should also feel comfortable performing anterior vitrectomy, because often the vitreous will come up around the equator of the lens. "Depending on what my suspicion is, in some cases it means doing the surgery in combination with the retinal surgeon in the event there's no support for the zonules and we have to do a full-scale pars plana vitrectomy," Dr. Ayres says. "That's my last resort. I would rather take the cataract out [using the] anterior-segment approach."



Focal loss of zonular support, shown here at around 7 and 8 o'clock, should be noted preop in order to ensure a good result.

A Bad Start

The beginning of the capsulorhexis is one of the most common times you'll identify zonular weakness that's not iatrogenic, making the capsulorhexis more difficult to complete.

As you begin the procedure and fill the anterior chamber with viscoelastic, look for a deepening of the chamber and focal areas in which the lens moves posteriorly or tilts. Consider using a heavier and more dispersive viscoelastic, such as Healon 5, which can help stabilize the eye and prevent vitreous from prolapsing around loose zonules. One precaution, however: Viscoelastics may put further pressure on the lens capsules and zonules, pushing the lens farther back and actually destabilizing the eye. "I'm cautious with the viscoelastic," Dr. Ayres says. "If I need to improve my view of the lens, [I use] iris retractors."

Once you insert the cystotome, a taut capsular bag will puncture and tear, and the lens will remain still, but in cases of zonular instability, the lens may move and you'll see wrinkles appear in the anterior capsule, Dr. Feldman says. As you approach that area and begin tearing the capsule, there's poor countertraction; rather than continue tearing the capsule and pulling on the zonules, at this point you might want to consider a CTR or a capsular support hook.

Rings and Anchors

Standard CTRs are sufficient in cases that involve only mild weakness or only a few clock hours of weakness. Furthermore, Dr. Snyder says, use of a standard ring in areas of focal weakness, perhaps from trauma, helps ensure that the capsular bag stays even or secure without the need for fixation to the wall of the eye.

Standard rings also are indicated for individuals who have no current zonular weakness but who have conditions associated with zonular instability and are likely to develop it in the future. Having a CTR in place now makes later repair easier. "It's much easier to stitch a ring for added security than it is to stitch an implant lens that doesn't have a ring in place," Dr. Snyder says.

If the patient has severe zonular instability, however, the capsular bag could be decentered. "In that case, we're better [off] using something to keep the bag tethered to the wall of the eye," Dr. Snyder says.

A modified capsular tension ring, such as the Malyugin/Cionni CTR (FCI Ophthalmics/Morcher), might be useful in such circumstances. Because this ring has a ring around the capsulorhexis and a hook that has a small eyelet, Dr. Snyder says it's possible to use a suture to affix the ring against the wall of the eye—creating a synthetic zonule of sorts.

Keep in mind that you can insert a CTR at any time during the procedure. "There's no real rule as to when that CTR goes in," Dr. Ayres says. "When you put those rings in, it can make cataract removal and cortical cleanup

more challenging, but you need them to increase the safety of the case. You try to put them in as late as you can. It depends on how the case is going."

In other instances, an Ahmed segment, in the shape of a 120-degree arc, might be a more appropriate choice, particularly if there is weakness in one area. However, if there is weakness in all areas, an Ahmed segment and a Cionni ring might be necessary. In cases of severe weakness, two segments may be required.

Other devices include the Malyugin Capsular Tension Ring (MicroSurgical Technology Inc.), which requires a smaller opening, and the AssiAnchor (Hanita Lenses), which you can insert into the capsular bag at 1.5 clock hours. In the latter device, the fixation piece is centrifugal, which allows the surgeon to exert torque on the capsular bag, unlike an Ahmed segment. "If you have an Ahmed segment or similar element in the equator of the capsular bag whose fixation tether is centripedal to the equator, [you] can induce torque, distort the bag and, sometimes, pull the element out of the bag entirely," Dr. Snyder says.

Removing the Cataract

Cortical stripping is another time you may discover zonular disease you were not aware of. "When you remove the cortex, that's when you have the most direct pressure on the zonules," Dr. Feldman says.

For patients who have pseudoexfoliation, Dr. Feldman uses a sweeping motion to pull the cortex aside and direct forces in a peripheral motion rather than centrally, which would put more focal traction on individual zonules.

After the capsulorhexis, Dr. Feldman says extra hydrodissection is important to ensure the lens is free from the bag and that you're not putting any torsion on the zonules. Dr. Ayres agrees, saying this allows the surgeon to rotate the lens material in the capsular bag to facilitate removal.

Splitting the lens into smaller pieces becomes much more difficult in individuals with zonular weakness, so Dr. Ayres chops the lens. "I lower all settings, pressures, and I use as much manual disassembly as possible. Instead of using phacoemulsification energy, I use mechanical energy to carefully remove the lens," he says.

Dr. Feldman recommends a vertical chop technique to avoid putting pressure on the capsular bag and to allow the lens to come out easily in small pieces. "If you take a large piece of the nucleus out of the bag, especially if it's one of the first segments you take out, if it catches on the anterior capsule or it's not separated from other nucleus, it could put further pressure on the bag, causing more zonular dehiscence," he says.

As you take out additional pieces, you may notice zonular instability that you weren't aware of. "If there are poor equatorial zonules, you'll start to see some of the extracapsular bag coming inward," Dr. Feldman says "The lens itself can act like a capsular tension ring; when you take that volume out, the capsule can fall in on its own."

Should this happen, you'll want to use dispersive viscoelastic to prevent posterior capsule rupture, Dr. Feldman says. Also, fill the anterior chamber with viscoelastic when you remove the phaco needle. "You never want the chamber to shallow. Otherwise you can make the instability even worse," says Dr. Ayres. He adds that, once the nuclear portion of the lens is removed, you may want to place a CTR if you haven't already done so.

The IOL

There currently is a debate as to what type of intraocular lens is most appropriate for patients with zonular instability. Dr. Ayres says he typically uses a single-piece acrylic lens that he can insert into the bag without any trauma. Another possibility is to place a three-piece IOL in the sulcus space.

"Many physicians will stay away from a premium IOL in these cases because there's so much unknown," Dr. Ayres says.

Experts say to keep in mind that if the patient has zonular instability due to pseudoexfoliation or if the patient is young, there's a chance the lens may dislocate within seven to eight years postop. "For patients who are younger, I'm more apt to suture the lens," Dr. Feldman says.

Also, when using CTRs, Dr. Snyder says to keep in mind that if you've secured the ring to the wall of the eye on one side, the zonules on the other side may become more unstable in the future. Also, polypropylene sutures may erode within seven to 10 years, requiring that the patient return to the OR for a patch graft. As a result, you probably want to avoid these in younger patients.

Postop Care

Because surgery on patients with zonular instability takes much longer, Dr. Ayres tends to use more steroids postop than he might in other patients. "As long as the cornea looks clear, I tend to put them on NSAIDs for six to eight weeks. Then you keep looking at them," he says. "Also, if a vitrectomy was performed, monitor the patient for retinal tears or potential detachment."

Cataract surgery in patients with zonular instability, though challenging, is an inevitability. "We're all going to deal with these patients," Dr. Feldman says. "And often it is a surprise. Every surgeon should be comfortable with getting the lens out in patients with zonular weakness, performing an anterior vitrectomy and having some go-to techniques to make sure the lens doesn't fall posteriorly." REVIEW

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It's (Not) in the Bag: IOL Fixation

Kristine Brennan, Senior Associate Editor

Choosing the best technique in the absence of capsular support can be tricky.

Conventional intraocular lens implantation relies on good capsular support. Sometimes, however, factors such as trauma, disease or complicated cataract surgery can make conventional in-the-bag fixation impossible. There are multiple ways to address inadequate capsular support, including anterior chamber IOLs and iris- and scleral-fixated lenses; there is evidence that they all have comparable benefits and risks.[1]

Here, cataract experts discuss their choices of IOL fixation in the absence of capsular support.

ACIOLs

Anterior chamber IOLs supported by the chamber angle require good endothelial health and a normal anterior chamber depth. "Advantages of this technique include the relatively quick operating time and the straightforward surgical procedure," says Kevin Rosenberg, MD, of Retina Vitreous Surgeons of Central New York and clinical assistant professor at SUNY Upstate Medical University. Modern flexible open-loop haptics and anteriorly vaulted optics help make ACIOLs beneficial for many patients, although they may be better suited to mature eyes.[2] "Though rarer now with better ACIOLs, uveitis-glaucoma-hyphema (UGH) syndrome still occurs. In addition, there is a possibility of cystoid macular edema occurring in these patients," Dr. Rosenberg adds. "I would avoid inserting ACIOLs in patients with a history of corneal issues, glaucoma, or in the setting of significant iris trauma."

George A. Williams, MD, chair of the Department of Ophthalmology at William Beaumont Hospital in Royal Oak, Mich., and clinical professor of biomedical sciences at The Eye Research Institute of Oakland University in Rochester, Mich., thinks many patients can do well with modern ACIOLs. "My exceptions are patients with endothelial compromise, glaucoma or diabetic retinopathy," he says.

"The decision regarding which type of IOL to use varies on a case-by-case basis, and there are certainly patients for whom I still find myself favoring an ACIOL," says Ehsan Rahimy, MD, a vitreoretinal surgeon with the Palo Alto Medical Foundation in California. He adds that the choice is dependent on multiple factors, including comorbidities such as glaucoma.

Garry P. Condon, MD, chair of the ophthalmology department at

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Allegheny General Hospital in Pittsburgh, and professor of ophthalmology at Philadelphia's Drexel University School of Medicine, believes that anterior chamber lens implantation is on the decline, but he also acknowledges that "a lot of studies aren't conclusively suggesting that anybody's suturing technique is better than a modern anterior chamber lens implantation." He says that surgeons are gravitating toward more posterior lens placement methods: "For patients who have lens implantations now, their expectations and our desire to deliver a more optically correct visual system are leading us away from anterior chamber lenses, where there are bigger incisions, a lot more astigmatism with suturing and a slower visual recovery."

Iris-Fixated IOLs

Dr. Condon adds that in his hands, an iris-sutured posterior chamber IOL procedure is more efficient than an ACIOL implantation. "My iris suture fixation technique requires a small incision, just two iris sutures and one corneal suture," he states. Dr. Condon helped lead the growth of iris fixation—historically indicated for repositioning dislocated lenses—in IOL exchanges and for aphakic eyes with poor capsular support. The advent of three-piece acrylic lenses promoted this shift. "We found that we could unfold the lens and actually capture it and do everything we would if that lens was a dislocated lens. That was certainly a nice option, considering that the other choices were either to put in an anterior chamber lens or place a big, single-piece, rigid scleral-fixed lens in the sulcus," he says.

Over many years of procedures, Dr. Condon has developed an ideal patient profile. "I like peripheral iris-sutured lenses in older patients with average-sized anterior segments, and in particular, those who still have some elements of capsule or vitreous present in the eye that help to stabilize the lens," he says, "We secure the haptic to the iris as peripherally as possible."

"The main advantage of iris-sutured IOLs is the ability to fixate a dislocated IOL to the iris without having to exchange the IOL," notes Dr. Rosenberg. "Disadvantages include the potential for causing a hyphema, either intraoperatively or postoperatively."

"As a retina specialist, I have seen patients with cystoid macular edema, recurrent bleeding or UGH syndrome following iris fixation," notes Dr. Williams. Dr. Condon concurs that iris suture fixation entails some risks. "The core of the uveal tract is there, and that's where the blood supply is, and it's susceptible to inflammation," he says. "It's very delicate when you're working with the iris, because it's so easy to tear it and make it bleed." Even a properly sutured iris-fixated PCIOL will have some mobility inside the eye, so the potential exists for mechanical trauma from pseudophacodonesis, which is one reason Dr. Condon generally avoids them in younger patients.

Dr. Rosenberg has concerns about suture longevity with this method. "Polypropylene, the suture typically employed in iris-fixated IOLS, may break over time, requiring yet another surgical procedure down the road," he notes.

"The suturing technique that I use is a modified McCannel suture, but utilizing a Siepser sliding knot for additional security," Dr. Condon says. "One of the problems that people have encountered is that while using a simple modified McCannel suture with both ends of the suture pulled up, the knot is tied on the outside of the eye," he says. "To secure the haptic to the iris, a simple modified McCannel suture, where the suture is brought outside the eye and tied, does not work as well as a sliding Siepser knot, where the entire knot slides into the eye more effectively. The risk of having the haptic slide through the suture knot is also less with the Siepser knot," he says.

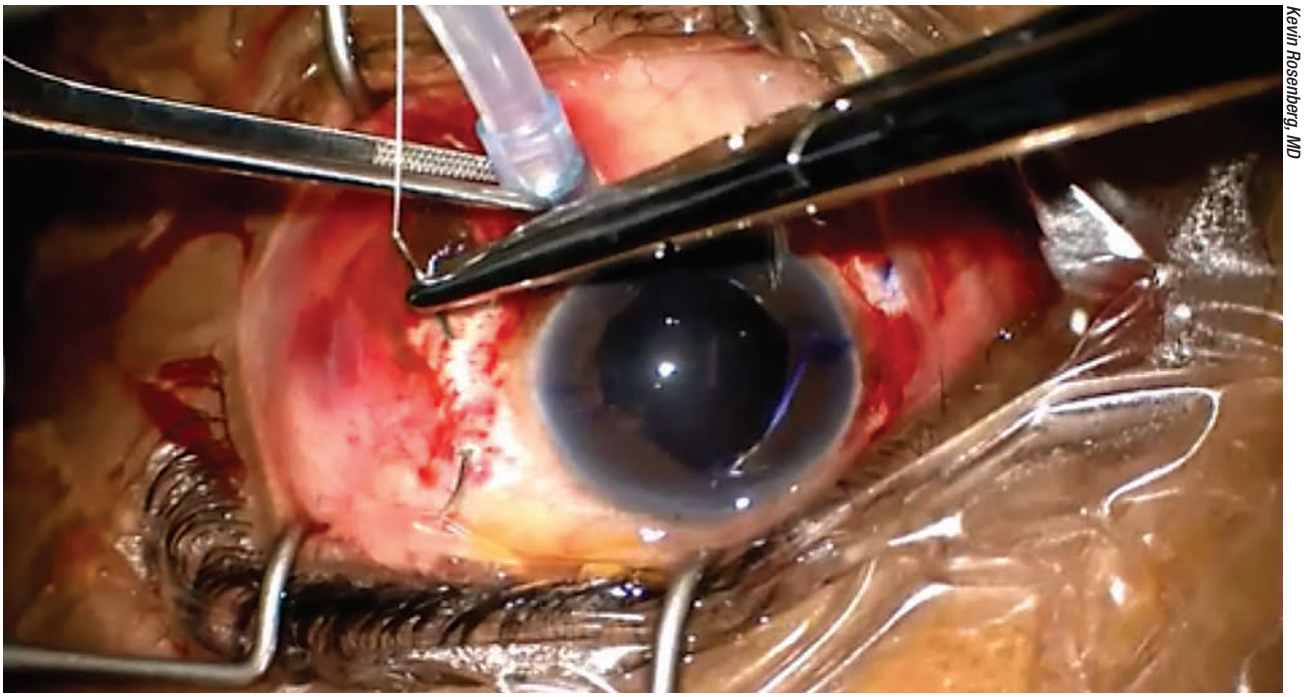
Dr. Condon doesn't alter IOL power calculations when using iris-fixated IOLs, because he says the effective lens position ends up approximating that of a conventionally captured IOL. "As Ike Ahmed and the folks at Moran Eye have demonstrated, when we prolapse the optic of the lens back through the pupil, the haptics commonly pop back behind the ciliary processes. This vaults the lens posteriorly, and also lends a little bit of stability to it because the haptics are now up against the back side of the ciliary processes," he explains. "That's why, in most cases where we do this technique, we recommend using the same lens power than we would use if we were putting it in the capsular bag."

Less commonly used in the United States, the sutureless iris-claw IOL is inserted through an approximately 5-mm incision and attached to the mid-peripheral iris using an enclavation needle to grab iris tissue between claws on either side of the lens while the pupil is constricted with a miotic.

A study of Artisan IOL posterior enclavation with two-year follow-up showed good visual outcomes, with no intraoperative and few postoperative complications.[3] Noting "interesting and encouraging results" with lobster-claw lenses in other surgeons' hands, Dr. Rahimy says, "I may potentially add this to my armamentarium in the future."

Scleral-fixated PCIOLs

Suturing an IOL to the sclera is perhaps more technically demanding



Kevin Rosenberg, MD

Suture pass using CV-8 Gore-Tex during scleral fixation. To mitigate the risk of infection arising from erosion of subconjunctival sutures, Jamin Brown, MD, has developed a novel Gore-Tex technique that results in a completely buried suture.

than the other techniques discussed here, but it has the advantages of durability and security, thanks in part to the haptic fixation points on PCIOLs.

Dr. Williams prefers trans-scleral fixation of the haptics of Alcon's MA60 or MA50, both three-piece PCIOLs. "When I suture, I use 10=0 Prolene with a CIF-4 needle (both Ethicon)," he explains. He adapts his approach to each eye, though. "The primary factors I consider are the type of IOL that is dislocated, the extent of the dislocation and the status of the capsular bag. For a partial dislocation of a one-piece IOL in the bag, I prefer trans-scleral suture fixation," he says. For complete dislocation of a one-piece lens including the capsular bag, however, he prefers replacing it with a scleral-fixated three-piece IOL. If there is retinal pathology, he will wait for the eye to quiet down before doing a secondary procedure. "I will leave the eye aphakic if there is an associated retinal problem, such as a retinal detachment that will require air or gas. Once the retinal detachment is fixed and stable, I will perform a secondary PCIOL placement via trans-scleral fixation," he says. Dr. Williams adds that for secondary scleral-fixated lens implantation, he typically calculates a lens power to target 1 D of myopia.

"If I have to put in or exchange an intraocular lens, I'm commonly going to a scleral-fixation approach, typically with the Akreos AO60, or the EnVista (both Bausch + Lomb) and Gore-Tex suture (W.L. Gore Medical; Elkton, Md.)," says Dr. Condon. "I like being able to put them through a small incision," he says. "I'll preload the lens with sutures and put it in the injector, and squirt it in the eye with all the sutures hanging out of the incision. Then I'll bring them in from the outside in, going through the sclera and pulling each suture in and out and then tying it." With the EnVista, he has taken to modifying the IOL. "Recently, I've been cutting the haptics off and just using the little hole in the haptic right next to the haptic-optic junction—loading that with strands of Gore-Tex, squirting the whole thing through a 2.4-mm incision and suturing it to the sclera, with zero in the way of astigmatism," he reports.

Dr. Rosenberg and Dr. Rahimy both consider scleral suturing of the Akreos lens with Gore-Tex their preferred method for eyes without capsular support. "This lens has four-point fixation and is therefore quite stable and the surgical procedure is straightforward," says Dr. Rosenberg. "The CV-8 Gore-Tex sutures are strong and easy to handle. In a patient without capsular support and a history of glaucoma, corneal issues, or iris trauma, this is definitely my technique of choice. Additionally, in young patients I prefer to implant these lenses, as opposed to ACIOLs, because I think they are probably a more stable long-term option.

"Despite its advantages, this technique is not without its drawbacks. After this technique the patient is left with a subconjunctival suture.

If the conjunctiva erodes postoperatively, then this suture serves as a potential route for bacteria to enter the eye and cause endophthalmitis," Dr. Rosenberg continues. "I am concerned with any technique that leaves suture or haptic in the subconjunctival space. In our group, we have seen both haptics and Gore-Tex erode through the conjunctiva, once resulting in endophthalmitis."

Dr. Rosenberg credits his partner, Jamin Brown, MD, with developing a Gore-Tex suture technique that sidesteps this risk and complication by completely burying the suture. "Essentially, the Gore-Tex CV-8 needle is passed partial-thickness between the sclerotomies as a first step, and then the suture is back-fed through the eye and the Akreos eyelets," he explains, adding that Dr. Brown's method also helps to prevent the sutures from getting tangled in the eye. (A video of the technique accompanies the online version of this article.) Dr. Rahimy, who with colleagues has published a step-by-step guide to his ab externo technique with the Akreos AO60 and CV-8 Gore-Tex[4] says that despite increased technical demands, "there is a rapid learning curve" to his method.

"Patient selection is key," he explains, "especially if this is one of your first times attempting this technique. You want to set yourself up for success. The relative ease, or difficulty, of handling the conjunctiva (especially closure at the end of the case) is an often overlooked, but critical, step that can make all the difference in terms of the case length as well as the surgeon's perception of the procedure's difficulty. Accordingly, preoperative conjunctival assessment is important, especially if the patient has had previous ocular surgery in which the conjunctiva was manipulated and may be potentially friable or scarred down, i.e., scleral buckling, multiple vitrectomies or a glaucoma filtration procedure with trabeculectomy or tube shunt."

Surgeons note some other factors to consider when approaching these cases:

• ***Handle haptics with care.*** "For the trans-scleral fixation technique using forceps, it is critical that the forceps engage the haptic as close to the end of the haptic as possible, and to slide the valved cannula up the forceps before externalizing the haptic," says Dr. Williams.

• ***Talk to patients about their visual expectations.*** Although this is crucial prior to any IOL implantation, Dr. Rahimy stresses the importance of realistic discussions in these complicated cases. "I explain to the patient that the targeted visual outcomes are a little less predictable with our secondary IOL techniques (especially if a lens is being removed and replaced), and that there is a high likelihood of needing additional refractive correction postoperatively, no matter how good their vision was before, when they had the in-the-bag IOL," he says.

• ***The line between anterior-segment and vitreoretinal skills is blurred***. "The pars plana is the most unappreciated anatomical part of the eyeball for the anterior segment surgeon," quips Dr. Condon. "We can go through it, we can tie things to it to scleral-fixate lenses. But to be versed in this stuff, you have to be comfortable with some pars plana vitrectomy work: That's where this goes beyond the scope of general anterior segment surgery. Comfort with the micro forceps and pars plana instrumentation is important if you want to feel comfortable doing scleral posterior chamber IOL fixation," he says.

• ***Beware IOL opacification.*** "The Akreos lens is hydrophilic, and there have been case reports of lens opacification of this IOL after intraocular gas use," cautions Dr. Rosenberg. "Therefore, some surgeons are wary of using this lens in a setting where gas may be used, as in retinal detachment repair or in a DSAEK procedure. I have used SF6 gas with this lens and did not have any postoperative lens opacification, but there is definitely the potential for this complication."

Glue-assisted Scleral Fixation

Fibrin glue and trans-scleral scarring, rather than sutures, secure the IOL in this method. Dr. Amar Agarwal, MS, FRCS, FRCOpth, chairman of the Agarwal group of eye hospitals in Chennai, India, has pioneered and refined the technique.[5,6] He performs only glue-assisted IOL implantations for out-of-the-bag fixation; he believes his method inhibits pseudophacodonesis better than ACIOLs or sutured PCIOLs. "Imagine if we glue a lens to a camera body: Both the lens and the body of the camera would move in unison," he says. " In the eye, potential movement of the IOL is thought to cause disturbance in the vitreous cavity, or in ACIOL cases, may cause release of inflammatory tissue from the iris, leading to prolonged CME," he says.

Dr. Agarwal uses the handshake method using two glued IOL forceps, after gently injecting a foldable three-piece IOL into the eye with one hand using an AMO injector. The surgeon always has hold of at least one haptic before each is bimanually guided into the proper sclerotomy. "Fear of the IOL falling into the vitreous cavity is not there, as the tip of the leading haptic is caught with the forceps, and the trailing haptic is still outside the eye," he says, adding, "The important step is to grab the tip of the haptic with the end-opening forceps," to prevent breakage and snagging during externalization.

Dr. Agarwal's "quintet" of pointers to optimize trans-scleral glued IOL surgery outcomes is as follows:

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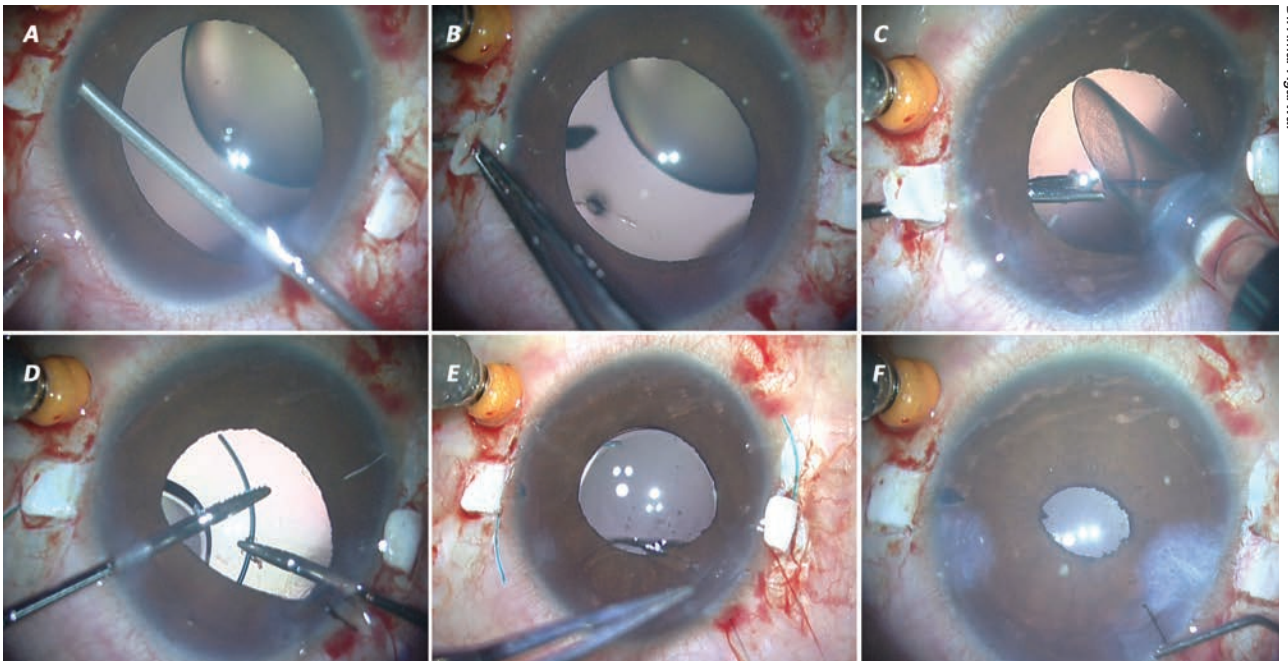

Dr. Amar Agarwal

Glue-assisted scleral IOL fixation in an eye with a subluxated lens due to Marfan's syndrome. A: Vitrectomy and peripheral iridectomy near scleral flaps. B: Anterior sclerotomy created with 22-ga. needle. C: After lensectomy, three-piece IOL in the AMO injector. The glued forceps is ready to grasp the haptic tip. D: Leading haptic externalized; two glued forceps used bimanually. E: Both haptics externalized. F: Haptics tucked in Scharioth pocket; fibrin glue applied.

1. Vertical glued fixation: In eyes with a white-to-white measurement greater than 11 mm, Dr. Agarwal makes his flaps at 6 and 12 o'clock, rather than 9 and 3 o'clock. "The vertical cornea will always be shorter than the horizontal, so one will have more haptic to tuck and glue," he says.

2. Infusion with trocar anterior chamber maintainer: "This allows continuous maintenance of the globe without encroaching upon the surface of the cornea, leaving the entire working space at the surgeon's disposal," he explains.

3. Peripheral iridectomy: Dr. Agarwal does this at the proposed sclerotomy sites, using a vitrector at 20 cuts per minute and low vacuum setting. "In large eyes it is advisable to do anterior sclerotomy," he says. Iridectomy keeps peripheral iris tissue clear of potential damage from the passage of the needle and forceps from the sclerotomy site.

4. Anterior sclerotomy: "The fourth part of the quintet is anterior sclerotomy performed 0.5 mm away from the limbus beneath the scleral flaps," says Dr. Agarwal.

5. Pupilloplasty: Dr. Agarwal says the last step of his quintet is "Single-pass Four Throw (SFT) pupilloplasty, negating any chance of optic capture."

No Clear Winner

Just as there are multiple causes of poor capsular support, there are many alternative ways to fixate an IOL that can produce good visual outcomes. Eye anatomy, ocular pathologies, visual potential and surgeon comfort are all guideposts in the decision-making process.[7] It's also important to be aware of situations in which a particular approach is comparatively contraindicated. "One must be adept at several different techniques and be willing to adjust plans on the fly during surgery," says Dr. Rahimy. "As one of my mentors in fellowship was fond of saying, 'Take what the eye gives you.' " REVIEW

Dr. Rosenberg is a member of Allergan's advisory board. Dr. Condon is a consultant and speaker for Alcon, Allergan and Microsurgical Technologies. Drs. Williams, Rahimy and Agarwal report no financial interests relevant to this article.

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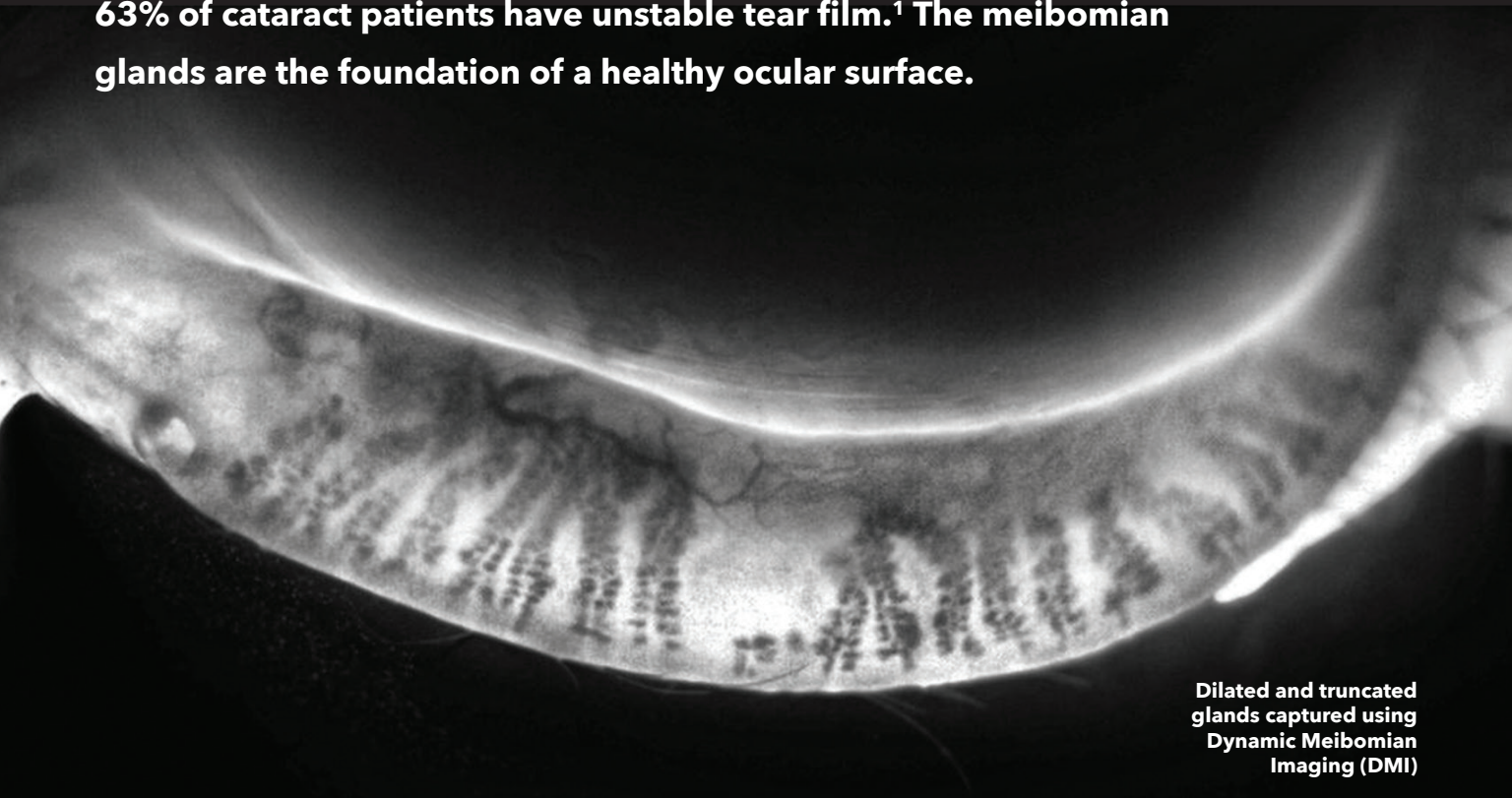
Are glands affecting your surgical outcomes?

63% of cataract patients have unstable tear film.[1] The meibomian glands are the foundation of a healthy ocular surface.



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Tips for Successful Anterior Vitrectomies

Walter Bethke, Editor in Chief

Surgeons explain how to get the best outcomes in these tough cases.

There's nothing worse than setting off in one direction, confident in your destination and how you're going to reach it, when all of a sudden you're forced to veer off-course in an entirely different direction, unsure of your surroundings or how to get back on course. The anxiety we feel in such moments is not unlike that felt when the cataract surgeon, to his growing dread, notices a tear in the posterior capsule and possible intrusion of vitreous in the anterior chamber. Fear not, though. Several anterior-vitrectomy experts are here to share the tips and techniques that can help you complete such cases successfully.

Warning Signs

Surgeons say to watch out for these early and late signs of trouble. Any one of them might mean an anterior vitrectomy is in order.

"Sometimes it's obvious the surgeon is going to have a problem," says Minneapolis anterior segment surgeon Sherman Reeves. "They can directly see that they've created a tear in the posterior capsule, or they see the tear occur during irrigation/aspiration. Other times, however, it's more challenging to identify, such as when the nucleus is being removed or during phaco in a very challenging cataract removal. Classic signs the surgeon can look for include a sudden deepening of the anterior chamber, which suggests that a posterior tear has occurred even though it might not be fully visible to the surgeon. Also, the iris may suddenly dilate, suggesting that a connection to the vitreous cavity has been created.

"Another sign is when the surgeon is removing lenticular fragments and he finds that the pieces aren't coming to the phaco tip as they should," Dr. Reeves adds. "The flow in the anterior segment is disturbed, abnormal. This suggests that vitreous is now in the anterior segment and is clogging the phaco probe. There could be an occult tear that the surgeon missed."

Lisa Brothers Arbisser, MD, adjunct professor of ophthalmology at the University of Utah's Moran Eye Center, lists a couple other late signs to be aware of:

- A nucleus that's mobile but then, suddenly, isn't mobile any longer, or develops a strange tilt.
- You touch one part of the tissue and another part moves. For instance, you touch the wound and see the iris move.
- The pupil is peaked or irregular.
- Your implant inexplicably won't center.
- An incision is well-made but won't

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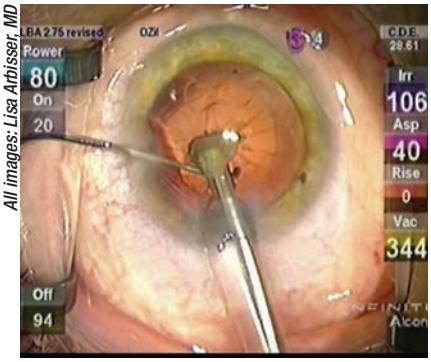
seal. It could have a tiny strand of vitreous passing through it.

Surgeons say that your initial reactions to these warning signs can make a big difference in how successful the case turns out to be. "When you notice or even suspect the signs of a posterior capsular tear, the most important thing is to stop but not pull away—the moment you pull an irrigating instrument out of the chamber it will collapse, enlarging the capsular rent and encouraging vitreous to move forward," advises Dr. Arbisser. "So, either stay in foot-position 1 or go to foot-position zero if the chamber is firm. Exchange the second instrument from the paracentesis for a visco cannula and fill the chamber with viscoelastic to maintain it. I prefer a dispersive viscoelastic but use whatever you have handy. Afterward, you can withdraw and inspect. The chamber should never be allowed to collapse again."

Dr. Arbisser says that, in the case of the warning sign Dr. Reeves described in which the nuclear material suddenly loses its followability to the phaco tip, you can take some action to minimize the negative implications. "If you have good followability that suddenly stops without any other change in fluidics, this can occur when vitreous, which is attracted to your phaco or I/A tip, occludes it, preventing nuclear material from following and entering the tip," she says. "This creates traction [on the retina] and the incarcerated vitreous should be sharply amputated with a scissor through the paracentesis, then reposited with OVD as the chamber is filled."

Dr. Arbisser says that the surgeon should remember he or she has options to enhance visualization if a posterior tear occurs and vitreous comes forward. "This complication sometimes happens in the setting of a small pupil or capsulorhexis," she says. "Don't hesitate to retract the iris with a Kuglen hook in order to see what's happening behind the iris. Visualization is everything. Iris hooks can also be placed, if necessary.

All images: Lisa Arbisser, MD



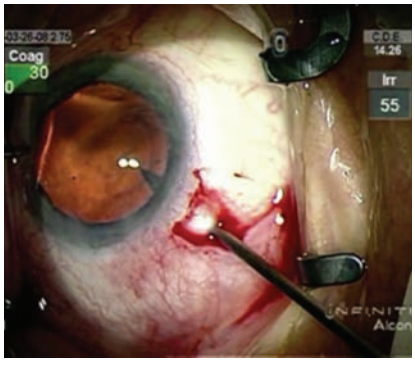
A "spider" on the posterior capsule signifies that a break probably occurred and that an anterior vitrectomy is needed.

"The most important goal, and the point of every subsequent maneuver after recognizing this complication," Dr. Arbisser continues, "is to prevent intraoperative or postoperative vitreous traction, which can lead to retinal tears and detachments, as well as cystoid macular edema. Also, keep a pressurized eye; hypotony or rapid, extreme pressure changes promote suprachoroidal hemorrhage, which can lead to permanently bad outcomes."

Anterior Vitrectomy

When you've confirmed that a posterior tear has occurred, here are the experts' tips on important aspects of your anterior vitrectomy:

• ***The incision.*** Some surgeons prefer an anterior approach while others like the advantages of a pars plana incision. "There are several good ways to approach it," says Dr. Reeves. "The key pearl is, regardless of an anterior/limbal approach or a pars plana approach, the main cataract wound should be closed. That wound should be abandoned—at least temporarily—for the purpose of the anterior vitrectomy because it's too large and would allow further vitreous prolapse through the wound. Therefore, it should be closed and probably have a suture put in it to further stabilize the anterior chamber."



For the entry stab incision, insert the blade until it's visible in the pupil, surgeons say.

Alan Crandall, MD, director of glaucoma and cataract at the Moran Eye Center, notes the hazards of using the main wound. "Some surgeons will put a vitrector through the main wound," he says. "But the wound is 2 to 3 mm, which is larger than the vitrector. This means there's flow coming out of the wound that will encourage things to constantly be moving forward in the eye and tug on the retina. You always want a separate port so there's a controlled anterior segment."

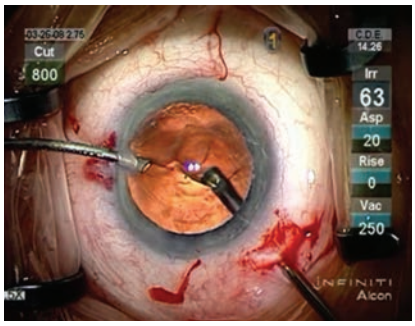
Dr. Reeves says he usually uses an anterior approach. "I make a second limbal paracentesis—I've already got one from the cataract procedure—and do a bimanual vitrectomy with an anterior approach after closing the main wound," he says. "I feel the limbal approach is a little quicker [than the pars plana approach] and less disruptive, because in most patients an unexpected capsular tear occurs under topical anesthesia, and it's easier to give them another drop of anesthesia, make another limbal paracentesis and not have to worry about increased discomfort from a pars plana approach and then needing to suture that.

"Another key pearl is that in order to perform the most effective anterior vitrectomy you can, the coaxial vitrectomy should be set aside and a bimanual approach taken," Dr. Reeves adds. "This applies whether it's a limbal or a pars plana approach. Using two ports—one for irrigation and the other

for the vitrector—gives the surgeon more freedom and access for vitreous removal, and also limits the size of the ports that are needed."

Although she agrees with the need for a bimanual approach, Dr. Arbisser is quick to extol the virtues of the pars plana. "Regardless of the approach you use, the incision must fit the bare vitrector needle, as vitrectomy is done biaxially with the irrigation performed separately," she notes. "It's safest to always keep the irrigation in the anterior segment, because you want to keep the pressure higher anteriorly than posteriorly, since vitreous will always follow a gradient from high to low pressure. However, even if you try to put a vitrector through an anterior paracentesis down through the hole in the capsule, this has a tendency to not only call back vitreous but to call it forward as well and to enlarge the capsular rent. Therefore, a one-port pars plana approach is more efficient, stabilizes the posterior capsule rent, and increases the chance of amputating any anterior/posterior connections so that, if we need to sweep or Weck the wound, we don't create traction."

She feels that the use of a trocar may be even more helpful, since it allows the surgeon to operate transconjunctivally and sutureless, and provides a conduit that sticks into the globe without working right at the pars plana internal wall. This decreases the risk of incarcerating vitreous in the wound, and lets the surgeon work without any trauma or risk of detaching the choroid. "To insert the trocar, there are certain things to keep in mind," Dr. Arbisser explains. "First, trocars require some pressure on the globe, so the globe has to be absolutely sealed. The trocar needs to be inserted parallel to, and 3.5 mm back from, the limbus. However, while a direct MVR blade incision is perpendicular to the limbus and sclera, with the trocar we're going to be parallel to the limbus rather than perpendicular to it for a millimeter or two at a 30-degree angle to the sclera before going straight in, so the incision is 3.5 mm back at a 30-degree angle to the sclera and limbus-parallel. The goal is a scleral tunnel incision that has a roof and floor that will seal well and not allow vitreous to exit."



For the vitrectomy, surgeons say to balance irrigation and linear vacuum with a flow rate of 20 cc/min. in foot-position 3.

• ***Vitrectomy.*** The surgeons say that it's important to use the highest cutting rate possible when going after the vitreous strands to avoid traction on the retina. "I start by cleaning any vitreous in the anterior chamber that's already prolapsed, using I/A mode," explains Dr. Reeves. "Using the highest cut rate your machine can handle puts as little traction on the vitreous as possible as you try to clean out the anterior chamber. Then, I move to the posterior chamber and, at a very high cut rate, try to do a nice, complete core vitrectomy. Again, using the bimanual approach allows you to switch sides with the vitrector to make sure you're getting the vitreous from all aspects of the anterior chamber and under the iris. Particular regions of interest are the subincisional areas, because those are where you'll tend to have a lot of vitreous prolapse." Surgeons say that, while in cut I/A, it's often a good idea to remove vitreous in foot-position 3, but change to foot-position 2 when you're not targeting vitreous but instead are just moving the vitrector, since this will avoid pulling vitreous with the instrument as it moves.

Surgeons say if the posterior tear is small, you may be able to create a posterior capsulorhexis and implant the IOL in the bag. "If there's a small rent in the capsule, and you think you can manage implanting your lens in the bag, you can attempt to convert it to a posterior capsulorhexis using Utrata forceps," says Dr. Crandall. "If you can do that, you can use a dispersive rather than cohesive viscoelastic because it will stay there while you complete your phaco."

• ***Handling nucleus and cortex.*** Since the capsular tear can occur at various stages of cataract surgery, surgeons say you may have to deal with nuclear fragments and cortex during or after your vitrectomy. Here are their tips for leaving a clean anterior chamber. "If it's a relatively small piece and I'm dealing with a capsular rupture, and the piece is still in the anterior chamber, I lower the bottle height significantly and use viscoelastic to bring the piece up," says Dr. Crandall. "Then, even if I had to enlarge the wound to 3 or 4 mm, I'd just express it through the incision. That way I don't have to risk going back in and hitting it with phaco. If it's a larger piece, then I bury my phaco tip in it and bring it up. Then, using a second instrument, or something like a Sheets Glide or a Bobbit Glide to act as a pseudo-posterior capsule to keep it from falling back down, I can phaco it." Dr. Crandall notes that sometimes nuclear fragments are hidden by the iris or are in the space between the iris and the anterior capsule. "As you start to clear vitreous, you may see these fragments come forward," he says. "You have to constantly watch for them. If you see one, and it's small enough, you can put visco in and bring it out. If it's soft, though, you can switch the vitrector to I/A cut mode and treat it like epinuclear material for which you use just a little bit of flow. You can even do this with a phaco unit sometimes. However, in these instances, since you've got the vitrectomy handpiece going, as long as it doesn't look

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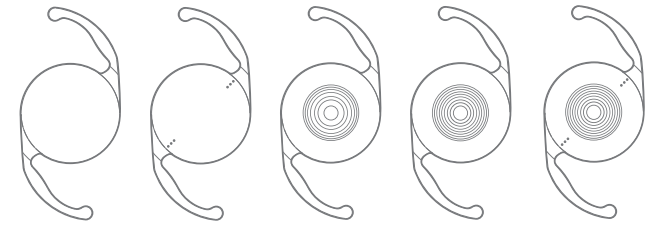

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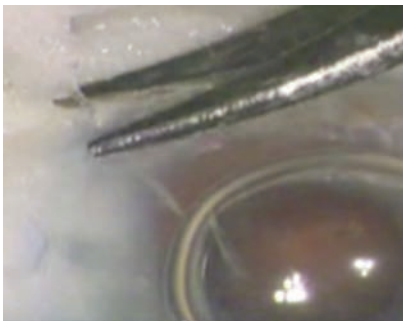

Lisa Arbisser, MD, says a wisp of vitreous will often be in the wound when an anterior approach is used for the vitrectomy.

like it's going to drop, you can bring it up into the anterior chamber and deal with it there using I/A-cut mode."

After the vitreous has been removed from the anterior chamber, surgeons say you can go after cortex. "After you've irrigated a small amount of Triessence [kenalog] into the anterior chamber and then blown it away with BSS irrigation, confirming the absence of prolapsed vitreous, you know you've reached your endpoint," says Dr. Arbisser. "You can then place a nice layer of dispersive viscoelastic over the rent, and keep the bag open with a cohesive OVD. You now have three choices for cortex removal: The safest choice is to do it dry—i.e., use a 26-ga. cannula on a 3- or 5-mm syringe, target a little cortex and then strip it away in a cohesive-OVD-filled environment. This is safest because there's no turbulence created. However, you have to keep filling the eye with OVD to keep it normotensive. Therefore, it's not very efficient if you have lots of cortex.

"The next option is to switch your vitrectomy settings from cut-I/A mode—which is used to remove vitreous—to I/A cut, in which foot-position 1 is still irrigation but foot-position 2 is aspiration," Dr. Arbisser continues. "Only when you go into foot-position 3 do you get cutting. This promotes cortical followability while allowing you to go into foot-position 3 to avoid traction should any vitreous appear. But doing so isn't that efficient because you have a 1-mm opening and, at least in a peristaltic machine, you need to have enough cortex occluding the port for removal. It's important to note that you never want to use vitrectomy settings for cortex removal because you will just eat away the cortex and follow it farther and farther into the capsular fornix, risking tearing up capsule. The point of your vitrectomy settings is to prevent followability (and therefore traction), but followability is our goal for cortex.

"The third, and most efficient, choice, is bimanual I/A," Dr. Arbisser says. "With this, you attach a bimanual aspiration handpiece but keep the irrigation anterior. This keeps the pressure superior so as not to encourage more vitreous to come forward. You can then target the cortex, keeping in mind that you can't allow the chamber to collapse, so you have to fill it with OVD before you come out. A meticulous cortex removal is valuable in these cases because they're prone to inflammation, CME and fluffing up of the cortex, which can fall into the vitreous or obscure the visual axis."

• ***Closing.*** Leaving a clean anterior chamber for any subsequent surgical intervention (such as by a retina colleague) is imperative, surgeons say.

"When you close the case, if you've left any nuclear material behind you want to place a stitch even if the wound appears stable and sealed," Dr. Arbisser avers. "You want to set the stage for the retina surgeon to be able to go in and remove the nuclear pieces. Since he or she is going to be using a trocar, you want the wound stable. If the wound doesn't seal easily, however, don't just place a suture. It may have vitreous incarcerated in it, so you'll need to instill Triessence to visualize any strands. Note that any sweeping or Wecking action will cause traction on the retina if vitreous is present. It's best to go back into the vitrector incision

(Continued on page 81)

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A Practical Approach to Canalicular Lacerations

Many periocular injuries involve the canaliculi. Here's how to assess the damage and successfully repair it.

Ann P. Murchison, MD, MPH, and Jurij R. Bilyk, MD, Philadelphia

Although periocular injuries can involve the canaliculi, the location and extent of the damage isn't always evident on gross examination. Getting to the root of the damage often involves a careful examination and probing of the lacrimal system. In this article, we'll discuss the techniques we use to successfully evaluate and treat canalicular injuries.

The Extent of the Problem

Ocular and periocular injuries can cause significant morbidity. The United States Eye Injury Registry has reported that periocular injuries occur in 5 percent of all serious injuries, with the majority involving the canaliculi (81 percent) and/or eyelids (70 percent). Not surprisingly, many of these injuries occur in children (23 percent) and teens (18 percent). Nearly half of periocular or ocular injuries (40 percent) occur in the home, most commonly from a blunt object (31 percent), and more than half (60 percent) of those with eyelid involvement have an underlying globe injury. A study performed by the National Center for Health Statistics estimated that more than 2 million eye injuries occur annually in the United States and about 90 percent of them are considered preventable.

Canalicular injuries result from penetrating injury or blunt trauma 54.2 percent and 45.7 percent of the time, respectively. Cadaver studies have showed that when a force is applied to the lateral canthus or malar eminence (as commonly occurs with a fist), lacerations will occur in the medial canthus because the medial canthal complex is weakened as it splays around the lacrimal drainage system. Such medial canthal injuries are frequently associated with laceration of the lacrimal drainage system (upper/lower canaliculus, common canaliculus, lacrimal sac). Of note, these lacerations often hide within the normal and complex three-dimensional anatomy of this area, and aren't suspected by the clinician because the blunt trauma occurred more laterally.

You should also maintain a high suspicion of canalicular involvement in lacerations medial to the puncta and secondary to dog-bite injuries. Canalicular laceration mandates primary repair. If not clearly evident, perform probing and irrigation of the lacrimal system to definitively confirm or rule out a canalicular laceration. *(See Figure 1)* A visible probe within the soft tissue laceration confirms the presence of canalicular injury. If probing can't be performed because of poor cooperation, then exploration in the operating room under anesthesia is indicated. A detailed anatomic description of the periocular structures is beyond the scope of this paper. However, a brief overview of the lacrimal drainage anatomy for quick reference is provided in Figure 2 on pg. 52.

Initial Assessment

The following steps are crucial for obtaining the correct diagnosis:

• ***Evaluation and history.*** Eyelid injuries frequently occur in the context of serious systemic or neurologic trauma. Severe head or facial injury often camouflages or supercedes occult ocular injuries, leading to a delay in diagnosis and therapy. A complete ocular examination is recommended in all patients with facial or head injuries once the patient is otherwise stable.

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Begin the evaluation with a complete history that includes pointed questions about the injury, including its mechanism, timing and location. This information can be a clue to any potential deeper injury, as demonstrated in a recent review in which half of eyelid injuries with intracranial involvement involved a fall onto a sharp object. The patient's allergies, tetanus status and last oral intake are important, and the patient shouldn't be allowed to eat or drink until the evaluation and any surgical planning are complete. Send out serum alcohol and toxicology screens in select patients if you anticipate the use of general anesthesia.

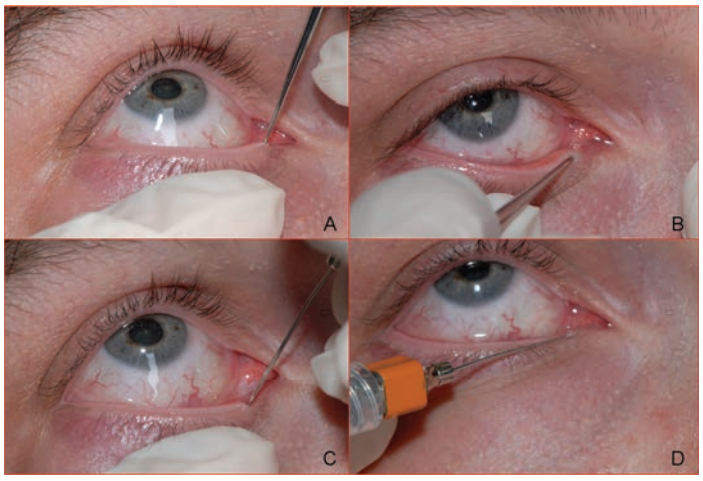

Figure 1. Probing and irrigation. After application of topical anesthesia, the clinician inserts a pediatric punctum dilator into the punctum vertically with a gentle rotating motion while applying lateral traction to the lower eyelid (A). The clinician turns the dilator horizontally and gently advances it, further dilating the punctum and proximal canaliculus. The dilator is then removed (B). Next, either a #00 Bowman probe or, as shown here, a straight lacrimal cannula attached to a syringe, is passed into the canaliculus, first vertically and then horizontally. Once again, it's critical to maintain lateral traction on the lid to prevent bunching of soft tissue. The examiner advances the cannula along the length of the horizontal canaliculus until bone (a hard stop) is felt (C). The cannula is pulled back slightly and irrigation is performed to confirm that nasolacrimal drainage is intact. If at any point the physician identifies the tip of the probe or cannula, a canalicular laceration is present (D).

Suppress the urge to begin the ocular examination with obvious clinical findings such as a lid laceration; instead perform a complete ophthalmic examination. During the ocular adnexal exam, avoid placing any pressure on the underlying globe until you've definitively ruled out globe injury. Note all the details about the lacerations, including the location, depth and any fat protrusion through the eyelid (which is an indication of orbital penetration). Any injuries to the medial canthus, even if trivial in appearance, raise the likelihood of canalicular involvement and necessitate probing and irrigation of the lacrimal drainage apparatus. This is especially common following periocular dog bites, which almost invariably lacerate one or more canaliculi.

To begin the probing procedure, administer topical ocular anesthetic (proparacaine, tetracaine or viscous lidocaine). Despite this maneuver, many patients will still experience discomfort during P&I, so you should warn them of this possibility. You then dilate the punctum with a pediatric punctum dilator and begin probing with a #00 Bowman probe or straight lacrimal cannula. Pass the probe vertically for 2 to 4 mm, and then rotate it horizontally toward the nose. Gentle lateral traction on the eyelid facilitates advancement of the probe.

• ***Imaging.*** Isolated eyelid lacerations with an otherwise normal ophthalmologic exam don't necessitate imaging, with several caveats. If you suspect a penetrating foreign body, perform computed tomography; avoid plain films, since they simply expose the patient to radiation without offering any detail as to the specific anatomic location of the foreign body. If you suspect a wooden foreign body, alert the radiologist to use the correct CT window setting, since wood is notoriously difficult to image. Magnetic resonance imaging may sometimes be helpful as adjunctive imaging in this situation, but should not be used as the primary imaging modality in trauma. A poor history also lowers the threshold for orbital imaging; this is especially important when evaluating children, who may be hesitant to admit to the true mechanism of injury with their parents listening nearby. Weigh the use of CT in children to exclude the possibility of occult foreign body against the risks of serial radiation exposure in the pediatric age group. If CT is indicated, match the protocol to the patient's age. Finally, it's important to remember that neither CT nor MRI are very sensitive for ruling out globe rupture (especially if no globe deformity is noted) and in no way supplant examination by indirect ophthalmoscopy or surgical exploration.

Surgical Intervention

If your exam and P&I reveal damage that requires surgery, here are the main points to keep in mind:

• ***Anesthesia.*** Canalicular injuries, frequently from assaults and dog bites, are generally isolated to the inferior canaliculus. Although there is controversy as to the relative importance of the lower versus upper canaliculus, be sure to repair any canalicular injury unless the patient decides otherwise. The timing of the canalicular repair is no longer guided by the historic

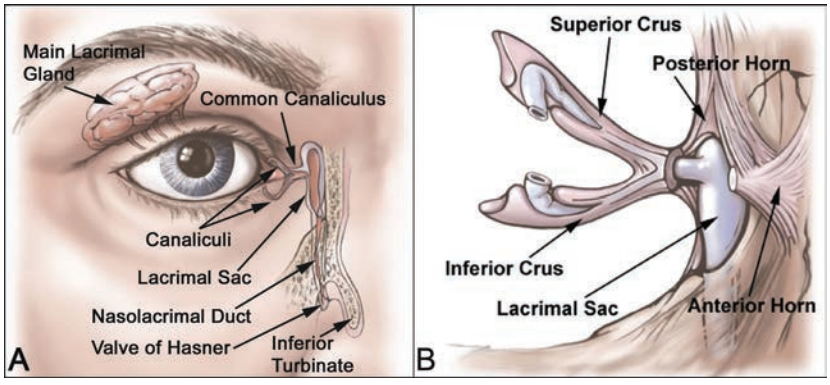

Figure 2. Lacrimal drainage anatomy: The complete lacrimal drainage system is shown, along with the main lacrimal gland. Note that the nasolacrimal duct opens at the valve of Hasner in the inferior meatus, under the inferior turbinate near the floor of the nasopharynx. The middle turbinate (not shown) is located just medial to the lacrimal sac and is encountered frequently during dacryocystorhinostomy, but plays no role in canalicular laceration repair (A). Medial canthal anatomy: Note how the anterior and posterior horns of the medial canthal tendon splay around the lacrimal sac to fuse with the periosteum of the anterior and posterior lacrimal crests, respectively. The main reparative vector of the medial canthal tendon should be aimed toward the posterior lacrimal crest to prevent medial ectropion (B).

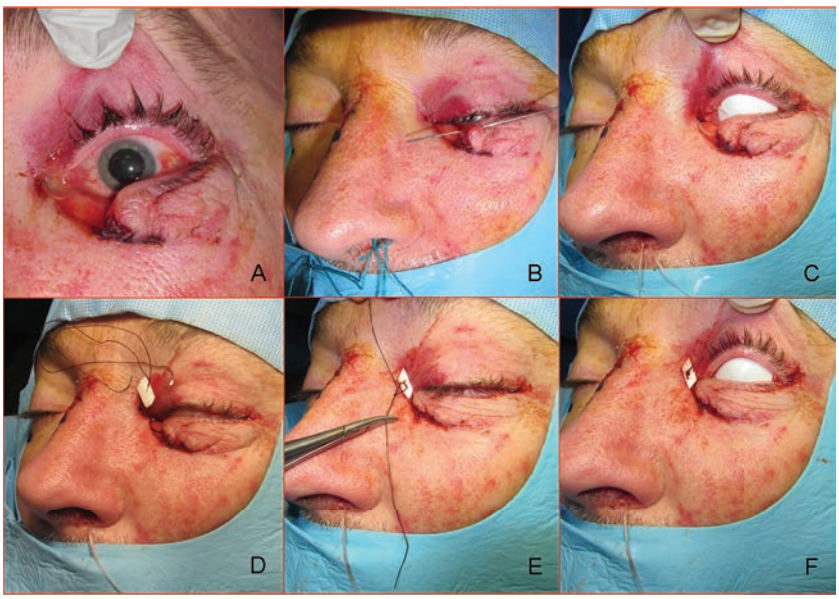

Figure 3. Surgical repair: Avulsion of the medial canthal tendon with an associated canalicular laceration from a dog bite (A). Passage of a Bowman probe confirms canalicular involvement. Once the distal segment of the canaliculus is identified, the physician passes the Crawford stent through the proximal canaliculus and then into the distal canaliculus and lacrimal sac (B). The entire lacrimal drainage system has been successfully intubated and both tubes have been externalized from the left naris (C). Repair of the medial canthus: A double-armed 4-0 silk suture on large needles has been passed through the pericanalicular orbicularis oculi muscle and externalized (D). The physician ties the suture over a foam bolster made from the suture packing material (E). Final appearance (F): The medial canthal suture is removed in seven to 10 days.

recommendation of six hours; successful repair five to seven days after injury is certainly achievable, but repair should proceed in a timely manner. We recommend repair within 48 to 72 hours.

Although canalicular lacerations very proximal to the punctum can be repaired successfully in the office or procedure room under local or regional anesthesia with a monocanalicular stent, the authors recommend that more distal injuries be repaired in the operating room under general anesthesia. Furthermore, while monocanalicular stents are quite effective for proximal canalicular repair, they're much more difficult to use for distal injury (i.e., injury closer to the common canaliculus and lacrimal sac) because distal injuries also usually involve some form of medial canthal avulsion. As the avulsed tendon is reapproximated, the monocanalicular stent tends to "accordion" in the soft tissue, precluding adequate reapproximation of the cut edges of the canaliculus. In such cases, some form of bicanalicular intubation is preferable, passing the stents down the nasolacrimal duct and externalizing them from beneath the inferior meatus; certain monocanalicular stents can also be passed into the nasolacrimal duct and retrieved from the naris. As you reapproximate the medial canthal tendon, you can place tension on the exteriorized stents and tubes, minimizing any bunching of the silicone tube. If you're going to use bi- or monocanalicular stenting through the nasolacrimal duct, general anesthesia is preferable. One final advantage of general anesthesia is that it precludes the need for a local anesthetic injection into the area of the medial canthus, minimizing soft tissue edema and distortion that can make identification of the distal end of the canaliculus difficult. If you deem the repair is appropriate for straight local anesthesia, use field blocks of the sen-

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sory nerves rather than direct injection into the traumatized area.

In addition to the anesthesia induction, nasal packing around the inferior turbinate at the start of the case with three oxymetazoline-soaked ½" x 3" neurosurgical cottonoids ("neuro patties") will shrink the nasal mucosa and facilitate retrieval of the silicone tube stents.

• ***Surgical repair.*** Begin repair of canalicular lacerations with copious irrigation and removal of particulates. If systemic antibiotics are indicated, such as for contaminated wounds, the maximum benefit is seen with administration within three hours of the original trauma. Generally, cephalexin is used, although penicillin V should be considered when an animal bite is known or suspected. Perform the standard prep with antiseptic solution; the use of povidone iodine solution is preferable to other preparations, since it is minimally toxic to the ocular surface.

Before you perform any debridement, explore the wounds and determine the proper positioning of tissue. Frequently, what appears to be significant tissue avulsion and loss is simply due to tissue retraction and edema. Because of the high tissue vascularity, it's uncommon to have to significantly debride the eyelids; however, any frankly necrotic tissue should be removed.

Exploration of an injured canaliculus is often frustrating, especially when the injury occurs deep within the medial canthal complex close to the lacrimal sac. *(See Figure 3A)* During exploration, many of the canthal tendon fibers convincingly mimic the cut edge of the canalicular mucosa. Several surgical maneuvers increase the likelihood of finding the distal canaliculus and minimize the risk of creating false passages that cause further injury to the soft tissue. First, the surgeon should avoid using an excess amount of local anesthetic infiltration. This is one reason why the authors have a low threshold for canalicular repair under general anesthesia, in which case no local anesthetic infiltration is used. Second, use cotton-tipped applicators for any exploration of the deeper soft tissue injury. The use of rake retractors and toothed forceps should be limited to skin retraction alone. The use of forceps during deeper soft tissue exploration results in further splaying and distortion of the medial canthal complex. Finally, the surgeon must resist the temptation to pass a Bowman probe in an impatient and haphazard fashion into soft tissue that looks like it might be the canaliculus. A gentle, blunt exploration, although more time consuming initially, will increase the likelihood of successful identification of the distal canaliculus.

Once you've identified the distal canaliculus, pass a #00 Bowman probe medially into the canaliculus and lacrimal sac. Successful passage will result in a hard stop as the probe reaches the bony lacrimal sac fossa abutting the medial wall of the sac. A soft stop typically indicates that you've made a false passage. If you create a false passage, remove the Bowman probe and perform additional exploration. If, instead, you achieve a successful hard stop, rotate the Bowman probe about 90 degrees along the superior orbital rim while maintaining gentle medial pressure against the lacrimal sac. As the probe rotates over the superior orbital rim, gently push it against the rim with the index finger of your other hand. Apply gentle pressure inferiorly with the probe as it passes the 45-degree mark, feeling for the nasolacrimal duct with the probe's tip. The nasolacrimal duct is usually accessible to the Bowman probe somewhere between the 45- and 90-degree rotation of the probe. While you're doing this, be sure to avoid applying vigorous force to avoid false passage into the nose. Once the probe enters the nasolacrimal duct, advance it gently just until it hits the floor of the nasopharynx. Additional pressure will simply force the probe more posteriorly in the nasopharynx.

At this juncture, remove any nasal packing. Pass a second, larger Bowman probe through the ispilateral naris beneath the inferior turbinate into the inferior meatus. This can either be done using direct visualization with a nasal speculum or endoscope, or alternatively, simply by feel—the authors' preferred method. It's important to remember that the nasolacrimal duct exit in the inferior meatus is located low and lateral within the nasal cavity. A tendency to look for the tip of the probe too superiorly and medially is common and should be avoided. A metal-on-metal scraping of one probe against the other indicates successful passage into the nasolacrimal duct.

Pass one end of the bicanalicular tube through the punctum of the involved eyelid and pull it out through the proximal cut end of the canaliculus. *(See Figure 2B)* While appropriate soft tissue retraction is performed by the assistant, gently back the Bowman probe out of the distal canaliculus and replace it with the stented tube, which you then pass into the lacrimal sac and down the nasolacrimal duct as just described. Then, externalize the stent and tube from beneath the inferior meatus and naris using any of a variety of methods, depending on the type of tube and surgeon preference. For example, the Crawford tube system uses stents with bulbous ends, which can be retrieved by passing a Crawford hook into the nose to engage the stent. *(See Figure 3)* The second stent is then passed through the uninvolved canaliculus and also exteriorized after being passed into the nasolacrimal duct.

With the canalicular system identified and intubated, further soft tissue repair ensues. *(See Figure 2C)*

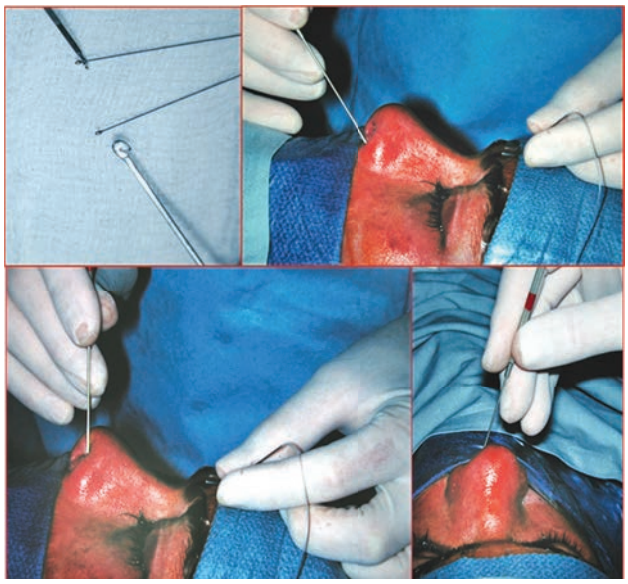

Figure. 4. Correct retrieval of a nasolacrimal stent. Top left: The surgeon engages the bulbous end of the Crawford stent with a Crawford hook. Top right: Incorrect positioning of the hook in the nose. Note that the hook is being angled superiorly, towards the middle turbinate. Bottom: Correct angulation of the Crawford hook is shown, staying low and lateral to pass the hook beneath the inferior turbinate into the inferior meatus.

Some surgeons will proceed with a meticulous—and admittedly frustrating—reapproximation of the canalicular mucosa with a fine suture, despite little evidence in the literature that this improves outcomes. We follow the recommendation of Robert Kersten, MD and Dwight Kulwin, MD, who advocate repair of the pericanalicular orbicularis oculi muscle, anticipating that the stented canalicular mucosa will heal adequately once reapproximated. One common technique we use to correctly reproduce the vectors of the medial canthal tendon (medial and posterior) is to pass a double-armed suture with large cutting needles around the pericanalicular orbicularis proximally, then distally, and continue the suture arc to skive along the periosteum medially, exteriorizing the sutures through the lateral nasal skin. *(See Figures 3D and E)* We then tie the sutures over a bolster and remove them a week later. *(See Figure 3F)* This avoids the need to tie a deep knot within the soft tissue of the medial canthal tendon. Typically, eyelid margin sutures are unnecessary. The scleral shell, which was placed over the eye at the start of the procedure, is removed before tying the tube to prevent tube migration. The final step is to place a hemostat at the level of the naris with gentle tension on the tube, cut off the stents, and tie the tube with one square knot, essentially forming a loop. The surgeon gently releases the hemostat and the tube retracts into the nasal cavity.

Complications

The overall success of canalicular repair is generally reported to be about 90 percent or higher. However, patients with canalicular lacerations can have epiphora even with careful repair. Epiphora after repair is likely more common with stent loss, stent extrusion, eyelid malposition or if no stent was placed; these issues can be avoided by individualizing the correct venue for repair (minor procedure room vs. operating room), choosing the correct anesthesia (field block vs. general anesthesia), and staffing by a surgeon experienced in canalicular laceration repair. Early, appropriate diagnosis and treatment can avoid or minimize many complications from canalicular injuries.

Other complications can also occur due to the initial injury and the wound-healing process. The relatively thin and complicated anatomy, coupled with the highly dynamic function of the eyelids, can lead to unique complications including eyelid malposition, eyelid margin notching, infection, scarring and lagophthalmos.

Eyelid injuries require a detailed examination of the globe and ocular adnexa prior to canalicular laceration repair. When performing lid laceration repair, your first priority should be to provide adequate protection for the ocular surfaces. When indicated, perform exploration of the adnexa, especially the lacrimal drainage system and the levator aponeurosis. Be sure to repair all canalicular lacerations whenever possible to minimize the risk of epiphora and other suboptimal outcomes. REVIEW

Dr. Murchison is the director of the Emergency Department, and Dr. Bilyk is an attending surgeon on the Oculoplastic and Orbital Surgery Service, at Wills Eye Hospital. They also provide care at Wills' Skull Base Division of the Neuro-Ophthalmology Service.

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What's New in Pediatric Corneal Transplants

A review of the advantages and disadvantages of our current options for corneal transplantation in children.

Mona Koaik, Carla J. Osigian, MD, Mohamed Abou Shousha, MD, Kara M. Cavuoto, MD, Miami

Due to monocular deprivation, corneal opacities in children can have a profoundly negative impact on visual development, leading to amblyopia and permanent visual loss. A keratoplasty may be indicated to provide a clear visual axis in these cases. Prior to the 1960s, however, corneal transplants were considered to be completely contraindicated in children.[1] Over the past 50 years, corneal surgeons have made substantial strides and have now developed a wide variety of procedures that can be performed safely in the pediatric population. These techniques include penetrating, anterior lamellar and endothelial keratoplasties, as well as keratoprostheses.[2-4] Although there's still a considerable risk associated with these procedures in children, they remain critical options for providing a clear visual pathway and mitigating the lifelong visual impediment of amblyopia.[4,5] In this article, we'll discuss the pros and cons of each approach.

Etiology & Clinical Challenges

The causes of pediatric corneal opacities vary by age group. In neonates, corneal opacities are likely secondary to primary corneal disease, whereas in older children they are mostly due to acquired traumatic and non-traumatic causes.[6] The etiologies are summarized in Table 1.

Obtaining an accurate assessment of the anatomy is one of the most important steps in the preoperative evaluation, as this will aid in diagnosis and prognosis. However, it's often difficult to obtain an adequate exam in younger patients due to limited cooperation, and an examination under anesthesia may be necessary.[7] Surgical interventions can be planned concurrently or at a subsequent evaluation. It's of the utmost importance to appropriately educate the child's parents or guardians regarding the frequency of postoperative follow-up with the cornea surgeon, as well as with the pediatric ophthalmologist for amblyopia management, in order to maximize the child's visual potential.[2-4,6]

Penetrating Keratoplasty

Traditionally, PKP was the treatment of choice for many corneal opacities. While older articles advised against keratoplasty in infants, recent literature recommends surgical intervention as early as possible to decrease the risk of amblyopia. This is particularly true in bilateral congenital corneal opacities, in which it's recommended to perform surgery within the first three months of life to allow for better visual rehabilitation.[3,4,8,9] In unilateral diseases, the chronicity of the condition, the risks of repeated anesthesia and the burden of prolonged postoperative care should be factored into the decision to proceed with surgery.[1,4,7,10] Here are the salient aspects of PKP in these patients:

• ***Intraoperative challenges and postoperative complications.*** The challenges of PKP stem from the mechanical characteristics of the child's cornea. Its reduced rigidity makes it prone to collapse intraoperatively, increasing the risk of iris-lens diaphragm prolapse during "open-sky" techniques. The small corneal diameter of the pediatric eye makes the intraoperative process challenging, as well. Other possible complications are summarized in Table 2.[4,11–13]

Most studies show a higher graft survival rate in patients with acquired

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opacities (up to an 85-percent one-year survival rate) when compared to the group with congenital opacities (50 to 90 percent).[10,11,14,15] In the group of congenital opacities, congenital hereditary endothelial dystrophy seems to carry the best prognosis, with a survival rate of up to 88 percent at one year.[14,16-18] It's suggested that the lack of anterior segment disease and/or corneal neovascularization in this condition leads to a more favorable outcome.[16] In contrast, other congenital forms, such as Peters anomaly, present a more variable one-year survival rate, ranging from 49 to 90 percent.[12,14,19–21] This wide range is thought to be secondary to the heterogeneity of this disease group. Peters anomaly type 1 has a milder presentation with no lenticular abnormalities and tends to have a high survival rate at one year.[4,20] Alternatively, Peters anomaly type 2 diffusely involves the lens and anterior chamber with a higher rate of associated ocular comorbidities such as glaucoma, which usually leads to a poor PKP outcome.[22] Lastly, the highest risk of failure is seen in congenital glaucoma and sclerocornea, with only a 50-percent chance of success.[5,17]

Table 1: Common Indications for Pediatric Penetrating Keratoplasty

Neonatal Corneal Opacities, Primary	congenital hereditary endothelial dystrophy	
	congenital hereditary stromal dystrophy	
	posterior polymorphous dystrophy	
	CYP1B1 mutation and corneal opacification	
	limbal dermoid	
	sclerocornea	
Neonatal Corneal Opacities, Secondary	kerato-irido-lenticular dysgenesis	Peters anomaly
		anterior segment dysgenesis
	irido-trabecular dysgenesis	congenital glaucoma
		intracorneal cysts
	metabolic	
Acquired, Traumatic	penetrating trauma with scarring	
	hyphema staining	
	corneoscleral laceration	
Acquired, Non-traumatic	keratoconus	
	bacterial keratitis	
	viral keratitis	
	post-infectious scars	
	keratomalacia	

Graft failure can occur at any point during the postoperative period, but happens more frequently within the first year post-transplant.[4,5] It can be due to a variety of causes, with the most common being rejection and infection. Children tend to have a more severe postoperative inflammatory response than adults, which increases the risks of synechiae formation and graft rejection.[1,3,4,9] The prolonged use of postoperative topical steroids is important to decrease the aggressive response, but it necessitates frequent assessment of the intraocular pressure.[23] Recent literature has demonstrated improved graft survival with the use of topical immunosuppressive agents such as cyclosporine, as compared to using topical steroids alone.[24] An additional advantage of these alternate immunosuppressive agents is that they don't carry the same risk of IOP elevation and glaucoma.

Graft survival isn't only affected by the type of opacity, but also by other intraoperative and postoperative variables. Several studies have shown that when PKP is combined with other procedures such as lensectomy/vitrectomy, the majority of children will eventually present with graft failure.[11,21] This highlights the high risk of failure in more severe cases needing multiple interventions at the time of PKP.[1,4,11,14] One study found that corneal neovascularization also suggests a lower chance of graft survival.[13] Additionally, glaucoma is an important consideration after PKPs. Studies have shown that its occurrence before or after transplant is a powerful indicator of graft failure, regardless of the status of IOP control. This is thought to be due to the endothelial cell damage that occurs with high IOP, predisposing the graft to rejection and failure.[2,14,23]

• ***Visual outcome.*** While most patients' visual acuities improve postoperatively, only 20 to 50 percent of pediatric patients undergoing PKP reach vision better than 20/80, despite good anatomic outcomes.[1,7] Earlier timing of surgery hasn't been shown to improve visual outcome; therefore, the timing of surgery should be considered on a case-by-case basis, taking into account the depth of amblyopia and the severity of the disease.[4,14,16] This highlights the importance of amblyopia therapy in the visual rehabilitation after a clear visual axis is achieved by PKP.[4,11] This process involves refractive correction with early contact lens fitting and suture removal as soon as a month postoperatively.[4,7,10] Since children are prone to accidental trauma,

Table 2: Complications of Pediatric PKP

allograft rejection
corneal scarring and neovascularization
iridocorneal adhesions
glaucoma
cataract
wound dehiscence
amblyopia
corneal steepening and high astigmatism
graft infection and ulceration
endophthalmitis
persistent epithelial defect
retinal detachment
phthisis

the eye may need to be shielded and the patients may need to wear protective polycarbonate spectacles.[1]

Anterior Lamellar Keratoplasty

ALK is a surgical procedure that involves the removal of the corneal stroma down to Descemet's membrane. It's indicated in corneal pathology that involves the anterior corneal layers but spares the endothelium.[25] Since the most common cause of graft failure after PKP is endothelial rejection, avoiding replacement of the endothelium dramatically improves graft survival.[5] Also, since the structural integrity of the eye is preserved in ALK, there's less risk of devastating complications such as expulsive hemorrhage or graft dehiscence.[26]

Recently, new advances in surgical instrumentation and techniques have managed to optimize the technique of deep anterior lamellar keratoplasty and have shown visual outcomes comparable to PKP but with a higher safety profile.[26] The different techniques in DALK include manual dissection, big-bubble technique and femtosecond-assisted anterior lamellar keratoplasty.[26-31] Manual dissection is the most basic technique; it involves trephination of the anterior stroma and its dissection from deeper layers using a crescent blade. In contrast, newer techniques involve using an air bubble injection into the deep stroma after trephination to create a plane through which to dissect.[26-29] Recent studies have looked at the use of intraoperative optical coherence tomography to guide DALK surgery, which would likely decrease the risk of perforation and increase the success rate.[31]

In the past decade, the introduction of the femtosecond laser has revolutionized corneal and refractive surgery. This technology, in conjunction with advances in corneal imaging, has allowed for the evolution of a new technique in ALK: femtosecond laser-assisted lamellar keratoplasty.[27,30] In FALK, anterior-segment OCT is used to determine the depth of the pathology and the lamellar cut in order to excise only the pathological tissue. The surgeon uses the laser to cut an identical donor corneal lenticule and uses it to replace the excised tissue, creating a smoother interface and yielding better surgical reproducibility. In cases where the corneal pathology spares a residual bed of 300 µm, the surgeon can place the donor corneal lenticule without a suture.[27,30] Despite the risks of corneal haze and residual corneal scars, the advantages of FALK remain its sutureless technique and rapid visual rehabilitation, with patients demonstrating an average gain of 2.5 lines in best-corrected vision postoperatively.[27,30]

• ***Considerations and outcomes.*** ALK is an excellent surgical option for children with anterior corneal pathology and a healthy endothelium. The literature has shown a dramatically decreased rate of graft rejection when compared to traditional PKP, with up to a 90 percent graft survival rate.[28] Nevertheless, this technique is challenging in younger eyes due to the elastic biomechanics of the cornea, which increase the risk of intraoperative corneal perforation and prolonged surgical time. These operative challenges, as well as the steep learning curve, have affected the popularity of ALK among corneal surgeons. Reported complications are similar to those found in adults, but occur with a higher frequency in children. Early postoperative complications are mainly micro-perforations and a double anterior chamber. Later complications involve graft dehiscence, astigmatism, loose sutures, keratitis, suture infection, graft-host interface haze, interface neovascularization and epithelial downgrowth.[26,27,29,30]

DSAEK

Endothelial keratoplasty in children was first reported in 2008. This technique involves scoring and removing the recipient Descemet's membrane, and injecting a donor membrane with its underlying healthy endothelium. An anterior chamber air bubble is then used to keep the graft in place without the need for sutures. In children, scoring of Descemet's may prove to be difficult, and some surgeons are avoiding this step by injecting the graft directly on top of the host's membrane, a technique called non-Descemet Stripping Endothelial Keratoplasty.[32] Current indications for DSAEK include: pseudophakic bullous edema; Peters anomaly; Descemet's membrane breaks induced by forceps delivery; posterior polymorphous dystrophy; buphthalmos due to congenital glaucoma; failed corneal grafts; and congenital hereditary endothelial dystrophy.[33-38]

• ***Considerations and outcomes.*** DSAEK is gaining more attention because it solves some of the problems with PKPs. It allows for a faster postoperative recovery, with earlier initiation of amblyopia treatment.[32] Additionally, DSAEK employs smaller, 4-mm wounds, which decreases the risks associated with open-sky techniques and also decreases the risk of infection. Suture-related issues are

also minimized. Importantly, postoperative refractive errors tend to be less than 3 D of astigmatism, which allows for a faster visual rehabilitation after surgery.[32,35,39,40]

Nevertheless, DSAEK in the pediatric population is very challenging. Technical difficulties of this technique include the difficulty of identifying and scoring Descemet's membrane, especially in infants.[32] Visualization of the anterior chamber is more difficult due to the presence of central corneal opacities.[32,34,41] Also, the anterior chamber tends to be smaller and shallower in pediatric eyes. Together, these factors make it harder to avoid lenticular injury during surgery. Additionally, the supine position required in the immediate postoperative period for the adherence of DSAEK grafts is often difficult for children to maintain. Thus, graft dislocation is a common complication and a challenge to treat.[32,35]

Keratoprosthesis

Keratoprosthesis is a procedure in which an artificial cornea is assembled with a donor corneal graft and sutured to the recipient cornea, providing a clear visual axis in a cornea that's otherwise opaque.[5] The first keratoprosthesis in an infant was performed in 2006 in a patient with Peters anomaly and congenital glaucoma who failed PKP.[42] Morbidity rates due to this procedure remain high; therefore it's currently only recommended in high-risk cases of failing PKP with risk of complete corneal blindness.[42] The main complications include retroprosthetic membranes, glaucoma, infection and endophthalmitis.[43] Keratoprosthesis remains a high-risk procedure, but its use may be beneficial as a way to prevent deep amblyopia from corneal blindness, until the patient is old enough to undergo a permanent graft.[5,43]

Though surveying the various options for pediatric transplants and their attendant advantages and drawbacks can be daunting, we hope this review helps to make the picture a little bit clearer. REVIEW

Ms. Koiak is a medical student at the University of Miami's Miller School of Medicine. Dr. Osigian is an instructor at the University's Bascom Palmer Eye Institute, and Drs. Shousha and Cavuoto are both assistant professors of clinical ophthalmology at Bascom Palmer.

The references for this article accompany the online version at reviewofophthalmology.com

Dry Eye: Beyond the Usual Suspects

Digging deeper into the types of patients who get dry eye and the situations that can bring it on.

Mark B. Abelson, MD, CM, FRCSC, FARVO, George Ousler, James McLaughlin, PhD, and David A. Hollander, MD, MBA
Andover, Mass.

You may have noticed the recent wave of advertisements regarding dry-eye awareness. Despite the central focus of these campaigns suggesting that only women over 40 years of age get the disease, it's worth remembering that other people get dry eye, too. Granted, many of the risk factors associated with dry eye, such as Sjögren's syndrome or systemic lupus erythematosus, are more common in women than in men. And we know that the protective effects of estrogens against dry eye underlie a surge in prevalence among post-menopausal women; all these phenomena lead to a clear gender bias. But along with its greater prevalence in women, another fundamental truism regarding dry eye is that it is underdiagnosed, and many of those overlooked patients are men, or they are young, or they are otherwise not of the same demographic group targeted in these advertising efforts. This issue is part of the larger problem faced in dry-eye diagnosis: While many patients have recognizable risk factors or co-morbidities, the challenge is that many of these undiagnosed or underdiagnosed patients may be part-timers: They are transiently symptomatic, or have what we refer to as situational dry eye.

It turns out that many of the factors that confound diagnosis and increase symptom severity can cause dry eye in people who don't have a chronic or ongoing condition. This month we take a new look at situational dry eye, specifically, its causes, treatments and what we believe is key to dealing with the condition: situational awareness. Confounding factors can be extrinsic or intrinsic, so it's important for us to be aware of both our environment and ourselves.

A Disease and a Condition

The signs of dry-eye disease result from a breakdown of the tear film involving one or more of its component layers (aqueous, lipid or mu-

Long-duration visual tasking, such as computer use or studying sets of images, can strain tear film homeostatic mechanisms and compromise the ocular surface.

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cin) and subsequent damage to the epithelial surface.[1-3] Factors leading to this surface damage include lacrimal or meibomian gland dysfunction, adverse responses to surgical procedures, irregular blinking and/or chronic ocular inflammation. Damage to the ocular surface ultimately impairs visual function, eliciting the characteristic dry-eye symptoms of burning, dryness and blurred vision, so these underlying causes of tear-film breakdown must be addressed as part of a comprehensive treatment.

Layered onto these internal issues are environmental and behavioral conditions that may either exacerbate ongoing dry eye or elicit situational dry eye. When faced with mounting adverse external stimuli, the homeostatic mechanisms that control a normal, healthy tear film are overwhelmed, leaving the ocular surface exposed. These environmental conditions include wind and low humidity, or particulates such as dust, pollen or pollution.[4,5] Indoor environments, especially where forced hot air is used for heating, present a low-humidity environment similar to the atmosphere in commercial airplane cabins, and can cause dry eye. The impact of reduced humidity on the tear film is twofold: It increases evaporation and reduces tear-film stability as measured by tear-film breakup times. Interestingly, it doesn't appear that the osmolarity of the tear film is significantly impacted.[6]

The importance of environmental factors in dry eye is underscored by the development of a useful clinical model, the controlled adverse environment.[7] In the CAE it's possible to modify relative humidity, air velocity and visual tasking under controlled conditions, using the triggers of situational dry eye to exacerbate the disease state in a precise and reproducible manner. Use of this CAE allows us to identify patients with significant, modifiable disease and to establish conditions under which we can precisely assess the ability of therapies to alleviate their signs and symptoms.

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When faced with conditions of high wind or glare, sunglasses or goggles are a good idea for everyone.

Most ophthalmologists would agree that dry eye is worse in winter, and a number of recent studies are confirming this empirical observation. Our own work has shown a significant seasonal difference for diary-reported ocular discomfort in clinical trials, with patients experiencing higher levels of symptoms during the winter. *(Ousler GW, et al. IOVS 2015;56:ARVO E-abstract 4462)* Others have shown a similar seasonality, although the underlying mechanisms may have some geographical variability.[8] The unifying theme is the impact that the environment can have on dry eye, and demonstration that natural (or artificial) environmental conditions can promote situations where dry eye becomes more prevalent and more severe.

Problems of Human Origin

One of the most significant extrinsic factors in situational dry eye is air pollution. In many parts of the world, air quality is so poor it can induce severe dry eye in eyes with even the healthiest of tear films. Ocular exposure to atmospheric pollutants such as ozone, automobile emissions and other byproducts of fossil fuel combustion causes both a physical and a chemical irritation that leads to elevated levels of free radicals and damage to ocular surface cell constituents.[9] A Korean study showed a strong correlation between increases in ozone levels and the symptoms of dry eye in a population of almost 17,000.[10] They also found a significant correlation between dry-eye symptoms and nitrogen dioxide, an airborne pollutant associated with automobile exhaust. These same pollutants are also known to elicit inflammatory responses in epithelial cells, including the corneal epithelium. This may be an important facet of pollution-induced dry eye.

One of the main issues dry-eye patients report is difficulty or discomfort associated with reading. Recent studies have focused on the causal relationships between dry eye and various visual tasks, including both traditional reading and the use of electronic visual media such as computers, tablets and smartphones.[11-13] Our own studies have shown that subjects with dry eye exhibit increases in blink frequency as a compensatory response while reading. In addition, many

dry-eye patients report an association between situational triggers such as wind, humidity and time of day with greater difficulty and discomfort with reading. *(Watson M, et al. IOVS 2014;55:ARVO E-abstract 1997)*

What about the impact of electronic media on dry eye? This is new territory in our understanding of both chronic and situational dry eye. It's worth noting that the first iPhone was released in June of 2007, after the publication of the seminal Dry Eye Workshop report.[4] One of the most interesting studies in this area, published last year, reported on the relationship between dry eye and smartphone use in school-age children.[14] The study looked at two groups of children, one from an urban environment and one from a rural area, and found significantly higher rates of dry eye in the urban group based upon the criteria of corneal staining, tear-film breakup and Ocular Surface Disease Index scores. A surprisingly high number of children (50 of 612; 8.2 percent) in the urban group were diagnosed with dry eye, while only 2.8 percent of 286 in the rural group met the same diagnostic criteria. The study also found significantly higher smartphone use in the urban group, and the average duration of phone use was significantly higher in those children diagnosed with dry eye. Perhaps the most noteworthy result from this study was that when children in the dry-eye group stopped using their phones for four weeks, the dry eye resolved completely: Tear-film breakup times improved significantly, corneal staining was reduced to negligible levels, and OSDI scores decreased from 30.74 ±13.36 points to 14.53 ±2.23 points ($p<0.001$). This suggests that their dry eye was situational, and that excessive visual tasking can act in the same way as wind, low humidity and pollutants in that it overwhelms the capacity of the tear film to protect against dry eye.

Responding to the Situation

There are a number of ways we can address the factors that lead to situational dry eye. Any activity or travel associated with exposure to wind or dust should trigger the use of protective eyewear such as sunglasses or goggles. For those of us living in northern climates, winter means lower humidity: wood stoves and fireplaces; and hot-air vents in homes, offices and cars. Humidifiers can make these closed environments more hospitable to a healthy ocular surface. Also remember that ocular allergy and dry eye often go hand in hand,[15] so any efforts to minimize dust, dander and pollen can alleviate both conditions.

Any activity or travel associated with exposure to wind or dust should trigger the use of protective eyewear such as sunglasses or goggles.

Beyond these extrinsic factors, other lifestyle modifications can ameliorate situational dry eye. Many medications, such as antihistamines, decongestants or pain relievers have ocular drying effects.[16] Hydration may be a factor, and one simple approach is to maintain an overall fluid balance.[17] Also, as demonstrated by the study of children and smartphones, it's important to be aware of the effects of visual tasking on your eyes; take breaks, alternate tasks and otherwise try to reduce long stretches spent staring at a video display. Despite advertising campaigns designed to target a single demographic, we're all potentially susceptible to dry eye. It just depends on the situation. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Mr. Ousler is vice president of dry eye at Ora Inc. Dr. McLaughlin 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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IMPORTANT SAFETY INFORMATION

Indication

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Contraindications

- ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- ILUVIEN is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.
- ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

- Intravitreal injections, including those with ILUVIEN, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.
- Use of corticosteroids including ILUVIEN may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.
- Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Adverse Reactions

- In controlled studies, the most common adverse reactions reported were cataract development (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of ≥10 mm Hg (ILUVIEN 34%; sham 10%).

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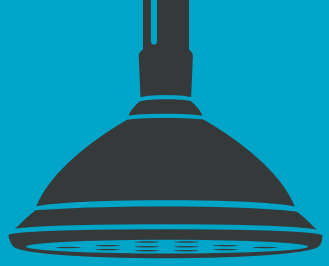

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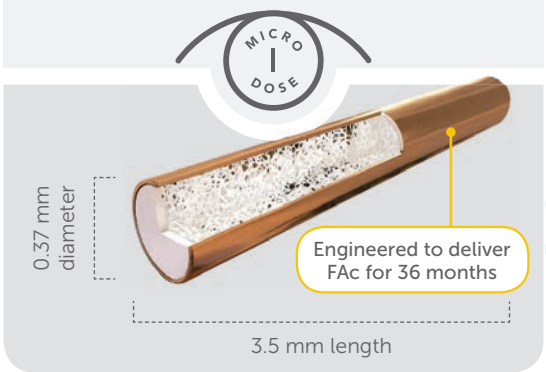

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1. Data on file. Alimera Sciences, Inc. **2.** Iluvien [package insert]. Alpharetta, GA: Alimera Sciences, Inc; 2014. **3.** Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626-635.e2. **4.** Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125-2132.

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ILUVIEN®
(fluocinolone acetonide intravitreal implant) 0.19mg

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

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INDICATIONS AND USAGE

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

CONTRAINDICATIONS

Ocular or Periocular Infections: **ILUVIEN** is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Glaucoma: **ILUVIEN** is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Hypersensitivity: **ILUVIEN** is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with **ILUVIEN**, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including **ILUVIEN** may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

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

Adverse reactions associated with ophthalmic steroids including **ILUVIEN** include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

ILUVIEN was studied in two multicenter, randomized, sham-controlled, masked trials in which patients with diabetic macular edema were treated with either **ILUVIEN** (n=375) or sham (n=185). Table 1 summarizes safety data available when the last subject completed the last 36-month follow up visit for the two primary **ILUVIEN** trials. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three-year follow up period, approximately 75% of the **ILUVIEN** treated subjects received only one **ILUVIEN** implant.

Table 1: Ocular Adverse Reactions Reported by ≥1% of Patients and Non-ocular Adverse Reactions Reported by ≥5% of Patients

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Ocular		
Cataract[1]	192/235[2] (82%)	61/121[2] (50%)
Myodesopsia	80 (21%)	17 (9%)
Eye pain	57 (15%)	25 (14%)
Conjunctival haemorrhage	50 (13%)	21 (11%)
Posterior capsule opacification	35 (9%)	6 (3%)
Eye irritation	30 (8%)	11 (6%)
Vitreous detachment	26 (7%)	12 (7%)
Conjunctivitis	14 (4%)	5 (3%)
Corneal oedema	13 (4%)	3 (2%)
Foreign body sensation in eyes	12 (3%)	4 (2%)
Eye pruritus	10 (3%)	3 (2%)
Ocular hyperaemia	10 (3%)	3 (2%)
Optic atrophy	9 (2%)	2 (1%)
Ocular discomfort	8 (2%)	1 (1%)
Photophobia	7 (2%)	2 (1%)
Retinal exudates	7 (2%)	0 (0%)
Anterior chamber cell	6 (2%)	1 (1%)
Eye discharge	6 (2%)	1 (1%)

Table 1 (continued)

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
Anemia	40 (11%)	10 (5%)
Headache	33 (9%)	11 (6%)
Renal failure	32 (9%)	10 (5%)
Pneumonia	28 (7%)	8 (4%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, cataract cortical and cataract diabetic in patients who were phakic at baseline. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery.

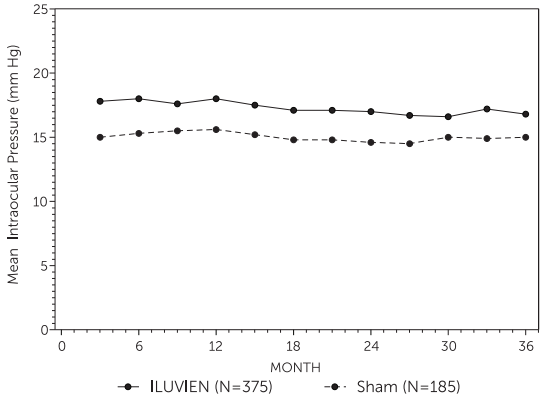
[2] 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 2: Summary of Elevated IOP-Related Adverse Reactions

Event	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
IOP elevation ≥ 10 mm Hg from baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mm Hg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

Figure 1: Mean IOP during the study



Cataracts and Cataract Surgery

At baseline, 235 of the 375 **ILUVIEN** subjects were phakic; 121 of 185 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the **ILUVIEN** group (82%) compared with sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the **ILUVIEN** group and 19 months in the sham group. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (Median Month 15 for both **ILUVIEN** group and for sham) of the studies.

Postmarketing Experience: The following reactions have been identified during post-marketing use of **ILUVIEN** in clinical practice. Because they are reported voluntarily, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ILUVIEN**, or a combination of these factors, include reports of drug administration error and reports of the drug being ineffective.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.
There are no adequate and well-controlled studies of **ILUVIEN** in pregnant women. Animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. **ILUVIEN** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of fluocinolone acetonide following intravitreal treatment with **ILUVIEN** is low. It is not known whether intravitreal treatment with **ILUVIEN** could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when **ILUVIEN** is administered to a nursing woman.
Pediatric Use: Safety and effectiveness of **ILUVIEN** in pediatric patients have not been established.
Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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Machine Learning for Diabetic Retinopathy

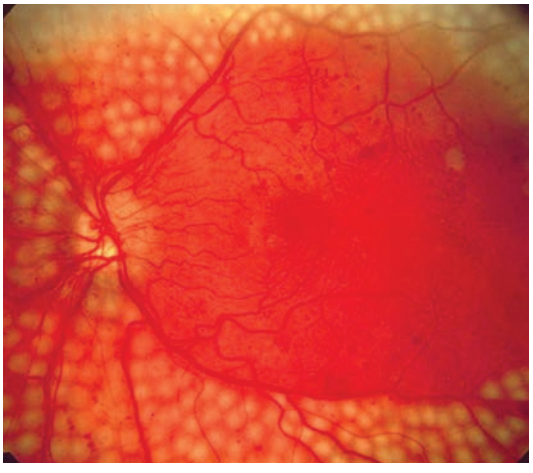
Adding computers to the mix may help ophthalmologists around the world catch and treat DR more effectively.

Peter A. Karth, MD, Stanford, Calif., and Ehsan Rahimy, MD, Palo Alto, Calif.

Late last year, *JAMA* featured a groundbreaking study by Varun Gulshan, PhD, Lily Peng, MD, PhD, and their colleagues at Google showing that the company's deep-learning algorithm could achieve the sensitivity and specificity of board-certified ophthalmologists when tasked with grading color fundus photographs of various stages of diabetic retinopathy.[1] The results raised a lot of eyebrows and put the medical world on notice that computer algorithms hold a great deal of promise for treating major diseases. In this article, we'll discuss how the study came about, its results and what the findings might mean for the care of diabetic retinopathy.

The Diabetes Epidemic

In 2015, the International Diabetes Federation estimated that 415 million adults have diabetes worldwide, and projected this number to grow by 50 percent to 642 million by 2040.[2] As many as 35 to 50 percent of all diabetics may have diabetic retinopathy.[3] Of those, 10 percent may be at risk for visual loss, meaning that up to 25 million people could be at risk of significant visual impairment.[4] Despite these dangers, however, a recent U.S. study noted that just 55 percent of patients with diabetes who were recommended for eye screening actually obtained a screening exam.[5] This figure is likely even lower in less-developed countries. Thus, the global need for improved access and adherence to screening programs is immense.



A computer system with high sensitivity and specificity could weed out cases that don't require treatment from those that do (above).

The Project Begins

During a trip to India, a Google employee (Google has not made the employee's identity public) was struck by the grave eye-care needs of the country's underserved population. The employee came back to the Bay Area with a passion for using Google's data-science capabilities to prevent vision loss—and the project was born. "The primary motivation for us is to improve access to low-cost, high-quality medical diagnostics, and to develop a technology that positively impacts everyone," says Dr. Gulshan, a senior research scientist at Google.[6] Over time, deep-learning technology has demonstrated real promise as a means to reduce vision loss.

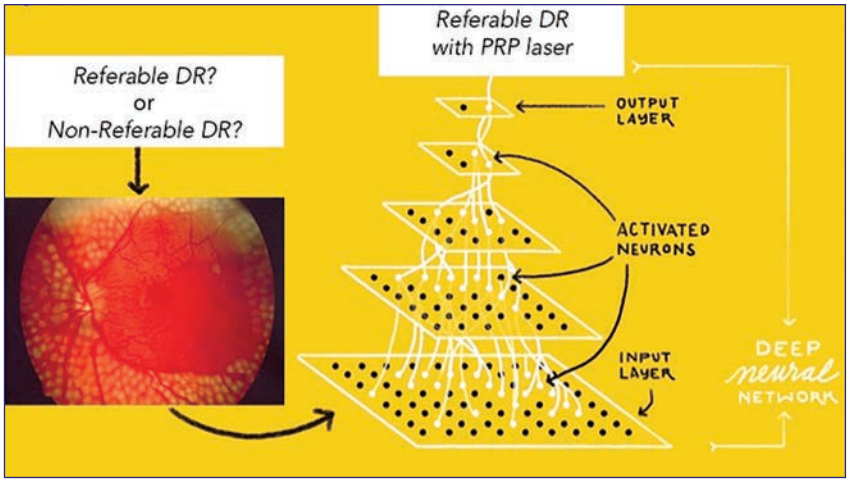
To understand the project, though, it helps to understand machine learning and a subset of it known as deep learning. Recently, the terms "artificial intelligence" and "machine learning" have become increasingly popular, although they're not synonymous. Artificial intelligence is a theoretical term referring to the

This article has no commercial sponsorship.

ability of a machine to accomplish tasks that normally require human intelligence. Machine learning, on the other hand, refers to a computer's ability to teach or improve itself via experience, without explicit programming for each improvement. Deep learning is a subsection within machine learning that focuses on using artificial neural networks to address highly abstract problems, like complex images.

The algorithm used in the Google study for automated diabetic retinopathy analysis is an example of deep learning. It's an advanced artificial neural network loosely modeled after the human brain. An artificial neural network is a computing system made up of a number of simple, highly interconnected processing elements.[1] The many nodes, or simple processors, within a neural network each perform simple calculations, which are weighted and summed to produce the final network output.

The Google system was first trained using hundreds of thousands of images labeled with a diagnosis by ophthalmologists. During the training phase, the system was initially presented with an image and it then made a guess as to what it might be. It then compared its answer to the ophthalmologists' labeled answer and adjusted the weight it gave to each node, learning how to compute with the lowest possible diagnostic error. It did this with hundreds of thousands of images. *(See Figure, above)* The number of nodes is restricted so that the system can't simply memorize the diagnosis for each image, but rather is forced to learn broad rules which are more likely to be generalizable to future, unseen images. "While it took immense computing power to train the algorithm, the eventual finished tool will be able to run on very basic computer hardware," notes study author Dr. Peng, a product manager at Google.[7]



Patterns are presented to the network via the "input layer," which communicates to one or more "hidden layers" where the actual processing is done via a system of weighted connections. The hidden layers then link to an "output layer" where the result is given.

More important, the Google deep-learning neural network doesn't include explicitly programmed feature recognition, which might look for retinal hemorrhages or cotton wool spots. Instead, the algorithm looks at every pixel of the photo and learns to recognize the severity of retinopathy using the full image. Currently, it's not entirely known which specific aspects of an image the algorithm is actually using to find the correct diagnosis, but this is an area of very active research by the team. It's interesting to consider that the algorithm may be using elements of the image that are different than those ophthalmologists use to arrive at the correct diagnosis.

When the Google team started the project, the initial task was to obtain a large library of fundus photos of diabetics for use in training the algorithm to recognize and grade diabetic retinopathy on color fundus images. For that, the Google team turned to existing large screening programs: 128,175 macula-centered fundus photographs were obtained from Eye Patient Archive Communication System, or EyePACS, in the United States and three eye hospitals in India (Aravind Eye Hospital, Sankara Nethralaya and Narayana Nethralaya). The images had 45-degree fields of view and more than half of them were non-mydriatic. Each of these images was then graded three to seven times by a group of 54 ophthalmologists, and nearly 10 percent of the images were randomly selected to be re-graded by the same physicians in order to assess intra-grader reliability. Images were assessed for the degree of diabetic retinopathy based on the International Clinical Diabetic Retinopathy scale of none, mild, moderate, severe or proliferative. Furthermore, visible hard exudates were used as a proxy for macular edema. This graded image set was then shown to the algorithm for training. Though the algorithm's accuracy leveled off at about 60,000 images, nearly twice that number were used.

Following the training phase, the system was validated by testing its diagnoses relative to a reference standard of ophthalmologists' assessments on tens of thousands of images it hadn't seen before (known as "out-of-sample" images). For this validation testing, the investigators used two sets of out-of-sample images (EyePACS-1 set = 9,963 images, and Messidor-2 set = 1,748 images). Each of these nearly 11,000 images

was graded by a minimum of seven board-certified ophthalmologists, and a majority opinion was taken as the Ground Truth. Ground Truth refers to the answer (or grade) taken as the "real" or correct answer, and to which the algorithm was compared.

In the two sets, when programmed for very high sensitivity, the algorithm achieved a sensitivity of 97.5 and 96.1 percent, and a specificity of 93.4 and 93.9 percent. Using an 8-percent prevalence of referable diabetic retinopathy in the population, these results yielded a negative predictive value (the probability that subjects who screen as negative truly don't have the disease) of 99.6 to 99.8 percent. Needless to say, these results were impressive.

What Does It All Mean?

The opportunities for artificial intelligence in ophthalmology are broad. The introduction of this kind of technology into the real world may increase efficiency and reduce the cost of screening and diagnosis. It may also increase consistency, considering the variability between physician graders that was seen in the study.

In health-care systems with few resources, there are clear benefits to machine-based automated diagnosis: We can unburden eye-care providers and clinics that are stretched too thin. We can also provide screening for those who might not otherwise be able to obtain it, for low or no cost. The importance of maintaining high specificity in the presence of high sensitivity cannot be overstated. Maximizing sensitivity goes a long way toward not missing patients with disease, but sacrificing specificity to achieve this yields overdiagnosis of disease, causing overcrowding of clinics with patients who don't need to be seen. Google's advanced algorithm appears to perform well on both fronts.

In health-care settings with ample resources, there are also opportunities. First, it's important to remember that there are large populations in the United States not being adequately screened for eye disease, especially diabetic retinopathy.[5] This means that a new low-cost, highly efficient screening system may reach people who are currently not being screened for eye diseases: Imagine the potential of screening kiosks in pharmacies and the lobbies of county hospitals. This could increase the total number of patients in the eye-care system while, at the same time, it could help keep patients with non-referable conditions out of the clinic, saving health-care dollars and maximizing ophthalmologists' efficiency.

The introduction of this kind of technology into the real world may increase efficiency and reduce the cost of screening and diagnosis.

Secondly, if the quality and breadth of the final system are sufficient, machine learning may be a diagnostic aid to eye-care professionals, improving the efficiency (and reducing the cost) of disease diagnosis and staging.

The Future

The future is bright for deep learning technologies in ophthalmology. With just a bit of imagination, we can envision a system in the future that diagnoses many different diseases and rules out any abnormalities, maybe even a multimodality total-eye diagnostic system. It's likely that this kind of system would lower the cost of early-stage eye care and could also reduce the burden and cost of eye disease overall.

For ophthalmologists and optometrists specifically, comprehensive automated diagnostic technology no doubt will cause changes to their fields, and the complexity of those changes is difficult to predict. For instance, these types of technologies may require ophthalmologists to focus more on management and patient education, and less on diagnosis. It's too early to tell at this point.

It's easy to let our imaginations run wild with this type of new technology, however. Right now, Google has shown it can diagnose and grade one disease in a study setting. We still have yet to see how this technology performs in the real world. Also, there are many diseases left to work on, not to mention the all-important task of catching life-threatening conditions in screening images, such as ocular melanoma. REVIEW

Dr. Karth is a vitreoretinal specialist at Oregon Eye Consultants and an adjunct assistant clinical professor at Stanford University. He can be reached at peterkarth@gmail.com; PeterKarthMD on Twitter, Facebook and LinkedIn. Dr. Rahimy is a vitreoretinal specialist at the Palo Alto Medical Foundation, and may be reached at erahimy@gmail.com; SFretina on Twitter. Both authors are physician research consultants for Google.

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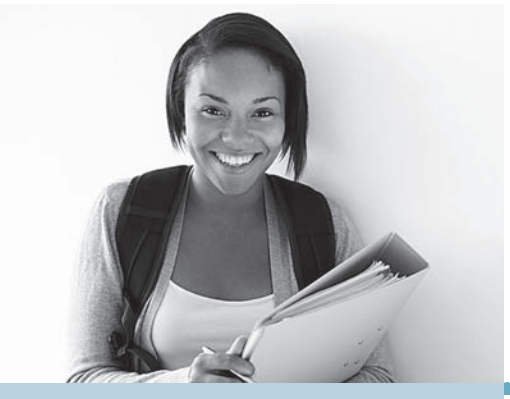

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Bringing Things Into (Tri)Focus

A primer on what may be the next wave of presbyopic intraocular lenses from overseas.

Walter Bethke, Editor in Chief

Attend any major ophthalmology meeting and you'll no doubt encounter presentations about trifocal intraocular lens technology, which builds on the principles of multiple foci in an effort to give patients better intermediate vision, in addition to the usual targets of near and far acuity. Though these new lenses haven't reached U.S. shores yet, the distant rumbling across the water usually means a storm will be here soon enough. Here's a review of the technology.

Trifocal Designs and Results

European surgeons familiar with trifocal intraocular lenses say that, like many technologies, trifocals grew out of the perceived shortcomings of previous generations of devices.

Thomas Kohnen, MD, professor and chairman of the Department of Ophthalmology, Goethe University, Frankfurt, Germany, describes the forces that brought about the new lenses. "Trifocal IOLs were basically constructed because we noticed over the years that with bifocal IOLs, the the intermediate vision was not strong enough," he says. "Patients complained about not being able to read the computer screen, and they could only read books at a very close distance or see objects in the distance—it was a major complaint. With this being the case, the idea of the trifocal lens came up, first with the FineVision lens (PhysIOL) and then with the Zeiss AT-LISA. With them, we finally had good trifocals." Since then, the Alcon PanOptix trifocal has also entered the market.

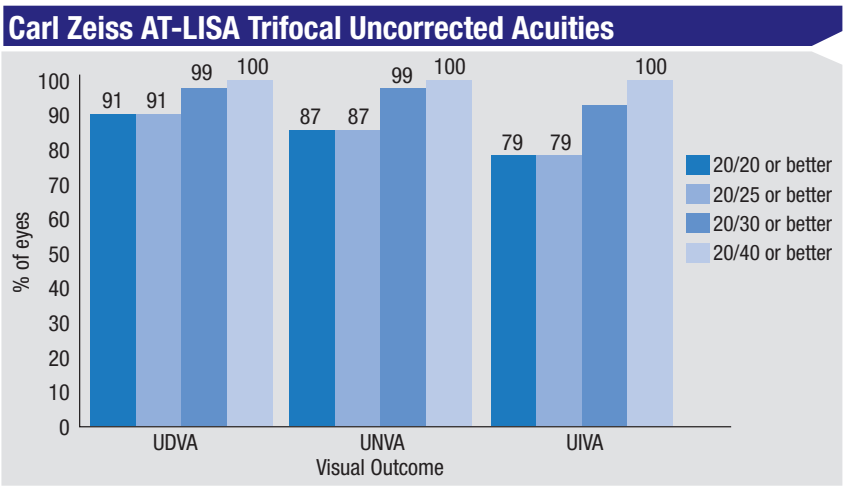
Milan, Italy's Francesco Carones, who's been involved with presbyopic lenses for years, and implanted the first Alcon ReSTOR toric lens in the world in 2010, says the trifocal design concepts are similar to their bifocal brethren but with a few key differences. "For multifocal IOLs, the focal distance is governed by the diffractive steps," he explains. "So the height of the steps and the distance between them generate the second focal point. With trifocal IOLs, instead of having one single height and distance, they have two repeating steps, one for intermediate and one for near, and they can spread this pattern over the lens surface as the PhysIOL or the Zeiss lenses do.

"Within the diffractive pattern on the lens, there's one flat area between the steps that redirects the light for distance," Dr. Carones explains. "So, for example, for the Zeiss and the PhysIOL trifocals, the amount of light energy is 33 percent for distance vision, 33 percent for intermediate and 33 percent for near. With the Alcon PanOptix, you have 50 percent for distance, 25 percent for intermediate and 25 percent for near. The additional 25 percent it gets for distance comes from that little flat area between the double-step pattern of the PanOptix."

The lenses differ slightly in where their focal points are set, as well. "For the PanOptix, Alcon changed the intermediate foci compared to the existing trifocal lenses," says Dr. Kohnen. "Instead of having an intermediate vision target of 80 cm like the PhysIOL and Zeiss lenses, the company changed it to 60 cm, which it thought was more appropriate after doing research into it for intermediate distances."

In addition to differing in the way they distribute light, these lenses also differ in their physical design, notes Florian Kretz, MD, director of EyeClinic Ahaus-Raesfeld-Rheine in Ahaus, Germany. "The AT-LISA is

trifocal in its center and bifocal in its periphery," he explains. "Specifically, the central 4.38 mm has a trifocal optic, and everything around it is bifocal. The near add power is 3.33 D, and the intermediate add is 1.66 D. In the periphery it's 3.33 D near. That means that, for this type of lens, the central trifocal part is pupil-independent for light distribution, and for larger pupils the distribution changes more at near than distance in order to enhance reading acuity under dim lighting conditions."



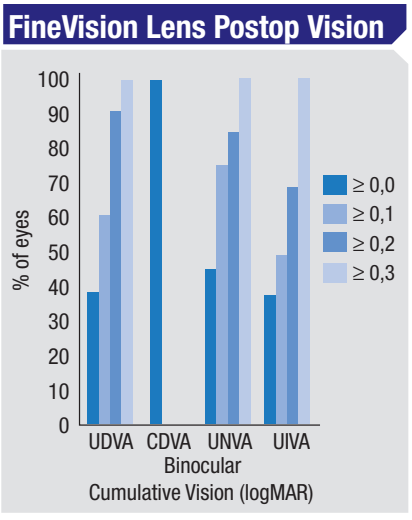
"The FineVision lens uses a different system," Dr. Kretz continues. "It's apodized over the entire surface. So the intermediate add power is 1.75 D, and the near add is 3.5 D. And due to the apodization there's less light transferred to the intermediate and near points at the periphery, so the lens enhances far vision more the wider the pupil becomes. With this design, there's also less straylight production."

Finally, in recent years the trifocal lenses have offered toric models, which Dr. Carones says is almost imperative. "The more complex the optics, the more you have to correct the astigmatism," he explains. "In other words, the more complex the optics, the less tolerant they are of astigmatism. So, for trifocals, when the astigmatism is greater than 0.5 D, it's quite mandatory to correct it, either through the IOL or through corneal incisions. Otherwise, you won't achieve a very good result, such as being able to bring patients to 20/20 uncorrected."

There have been a couple of studies published on the PhysIOL and Zeiss lenses, but the PanOptix is newer, and so data on it is still being gathered.

In a prospective study of the FineVision lens, Spanish researchers achieved an average binocular best-corrected distance acuity of a little worse than 20/16; a binocular distance-corrected intermediate acuity between 20/25 and 20/32; and distance-corrected near vision that was a little better than 20/25.[1]

In a prospective study of the Zeiss AT-LISA lens performed by Dr. Kretz and his colleagues, all patients had a binocular uncorrected distance visual acuity of 20/20 or better and a binocular uncorrected intermediate visual acuity of 20/25 or better, three months after surgery. Furthermore, 85 percent of patients achieved a binocular uncorrected near visual acuity of 20/25 or better.[2]



In a non-peer-reviewed study Dr. Kretz took part in, he says that, at least preliminarily, the PanOptix lens is promising. At 12 weeks in eight binocular implantations with the PanOptix, the average uncorrected distance acuity was between 20/20 and 20/32, the average intermediate vision was between 20/20 and 20/40 and the average near vision was between 20/25 and 20/40.

When the subject of presbyopia-correcting IOLs comes up, it's always accompanied by the shadow of photic complaints. However, reports seem to indicate these may not be worse in trifocal lenses than in bifocal multifocal IOLs. In a paper on the AT-LISA that Dr. Kretz co-authored, the mean scores (0 = no symptoms; 40 = strong symptoms) for night glare, ghost images and halos were 15.15 ±12.02, 4.49 ±7.92 and 13.34 ±10.82, respectively.[3]

"Among the three competitors: the Zeiss, the PhysIOL and the PanOptix," comments Dr. Carones, "I haven't seen significant differences in glare and halo. So I wouldn't say this is a criterion for deciding which one to implant." REVIEW

Drs. Kohnen and Carones are consultants to Alcon. Dr. Kretz consults for Carl Zeiss Meditec.

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Is It Glaucoma? Or Just High Myopia?

Highly myopic eyes often resemble glaucomatous eyes, so if pressure is normal, diagnosis can be challenging. Here's help.

Robert T. Chang, MD, Stanford, Calif.

One of the challenges anyone managing glaucoma will face from time to time is the dilemma of diagnosing and managing highly myopic patients who appear to have glaucoma, but don't have elevated eye pressure. High myopia can be associated with elongation of the eye and resultant tilting and torsion of the optic nerve head, causing visual field defects that may resemble glaucomatous damage, but are the result of myopia. This can make an accurate glaucoma diagnosis challenging, since there's no biomarker for disease. Preventive treatment can be expensive and bothersome and have potential side effects, so how should one approach a patient like this?

High myopia is increasingly common, and more middle-aged people have unusually shaped nerves as a result. In the Bay Area, we now commonly see middle-aged Asian myopes without high eye pressure who have glaucomatous-like visual field defects discovered during screening or by the patients themselves.

Here's what you should be thinking about when managing a relatively young, highly myopic patient like this.

Why It's a Challenge

Diagnosing glaucoma in a patient who is highly myopic and has anomalous nerves and an abnormal visual field but normal pressures is a problem. That's because we have three main ways to assess glaucoma: changes in the nerve, which can be measured by fundus photos and OCT imaging; changes in the visual fields indicating a progressive glaucomatous loss of visual function; and elevated intraocular pressure, which is currently our main modifiable risk factor for the disease.

Unfortunately, it can be difficult to identify the classic optic nerve changes for glaucoma in these highly myopic patients, and the fact that the pressure isn't elevated is inconclusive, because glaucoma can still occur at "normal" pressures. Finding a worsening visual field in a specific pattern over time would certainly suggest that the patient has glaucoma; but by the time the patient's visual fields have worsened, you've already lost the opportunity to prevent irreversible vision loss. Given that a correct diagnosis before visual field damage emerges is difficult at best, some myopes are probably being overtreated while others are being undertreated.

Matters are complicated even more by data showing that myopic refractive error is associated with glaucoma at a population level. Several large-population-based studies using different definitions of high myopia, including the Blue Mountains Eye Study, the Beijing Eye Study and the Los Angeles Latino Eye Study, have found that myopes are more likely to have glaucoma. The Blue Mountains Eye Study was criticized on the grounds that cataract-associated myopic shift was not taken into account; however, the Los Angeles Latino Eye study did correct for grade of cataract and axial length, and that data still demonstrated an association between myopia and glaucoma (in this study, myopia worse than -3 D). Of course, cross-sectional glaucoma diagnoses can be tricky, especially with myopic nerves, so it's possible that some myopes were misdiagnosed as having glaucoma, for

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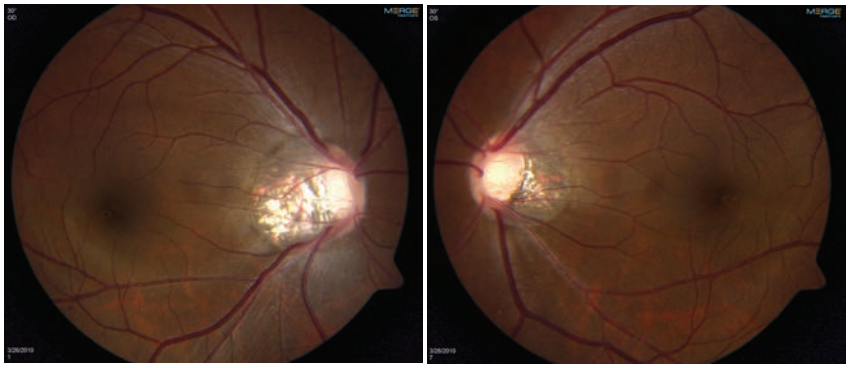


A young myope with abnormal-looking discs but normal intraocular pressure, open angles and no signs of secondary causes of glaucoma. Both nerves are oval and tilted, with significant temporal peripapillary atrophy.

the challenging diagnostic reasons we've been discussing.

To help shed some light on how often glaucomatous-like visual field defects occur in high myopes, my colleagues and I conducted a prospective study of the visual fields of 487 young high myopes in the Zhongshan Ophthalmic Center-Brien Holden Vision Institute High Myopia Registry Study, to learn more about the kind of field defects myopes tend to have.[1] A review of 1,434 visual fields (including repeat fields performed to confirm abnormal defects) found that 16.1 percent of defects in the subjects mimicked classic glaucomatous defects, while 3 percent of the eyes had defects that looked like the dense arcuate defects you'd find in moderate to advanced glaucoma. The study group did include a few glaucoma suspects, but most were healthy high myopes. We're currently following these individuals to see how many of them show true change over time; then we'll isolate features that were associated with glaucomatous field loss.

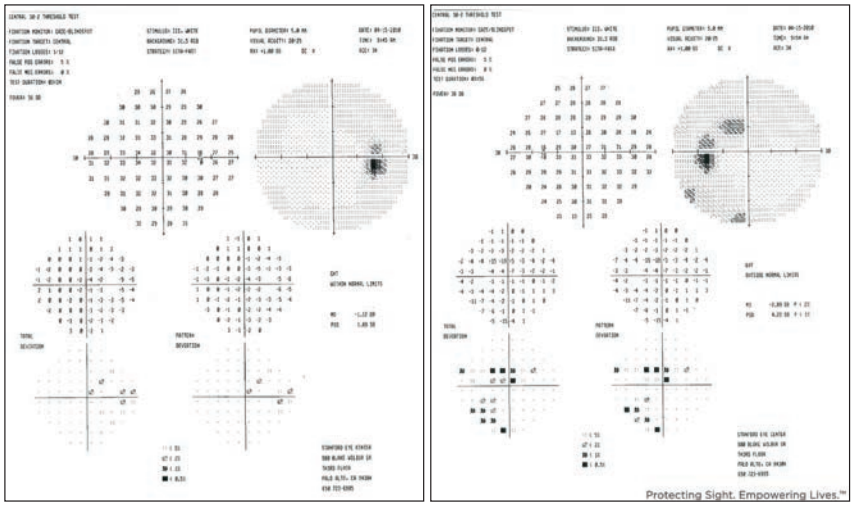
A Case History

A 35-year-old Asian woman presented to our glaucoma clinic for evaluation about six years ago. She was a -8 D myope in both eyes and had 20/20 vision with contact lens correction. She had no prior laser or surgical interventions and wasn't taking any ocular medications. She was aware that she had some family history of glaucoma, but didn't know the details. Her pressures were normal, 18 mmHg in both eyes; her corneal thickness was slightly above average; she had open angles and a normal exam and didn't show any signs of secondary causes of glaucoma. However, her optic nerves were very abnormal looking. *(See images, above.)* The nerves were both very oval and tilted, especially in the right eye, and there was significant temporal peripapillary atrophy in both. More concerning was a thin retinal nerve fiber layer defect in the right eye inferiorly. The left eye also had a large amount of nerve fiber layer loss, more inferiorly and nasally. The vessels were pushed far to the periphery, so the cup-to-disk ratio looked enlarged in both eyes, but it was difficult to assess the neuroretinal rim. Her optic nerves had features that could be attributable to either myopia or glaucoma.

Generally, when faced with a patient like this, you'd want to see the patient's visual field defects. *(See visual fields, below.)* In this patient, you can see an abnormal field defect in the left eye; the right eye doesn't have much of a defect. Given these fields in a myope without elevated eye pressure and no longitudinal data, I approached the patient as a glaucoma suspect and decided to proceed with preventive treatment. (I'll review her six-year follow-up at the end of this article.)

To Treat or Not to Treat?

One way a definitive diagnosis can be confirmed is by detecting measurable change indicating a glaucomatous rate of progression—hopefully a small enough amount of



Visual fields from the young myope shown above. The right eye had a thin retinal nerve fiber layer defect inferiorly, while the left eye had significant NFL loss inferiorly.

change that the patient won't have lost any visual function. However, in many cases simply accumulating enough risk factors and/or test results may justify the treatment choice. Thus, the more information you have, the better. With that in mind:

• ***See if OCT nerve fiber layer/ganglion cell analysis can provide additional information.*** It's important to factor in your OCT findings when evaluating the amount of vision the patient has left. That's true for two reasons: First, damage on OCT can precede visual field defects, so an OCT scan often may reveal damage that isn't evident on the visual field. Second, a visual field defect could be an artifact; comparing it to OCT data should help to clarify whether the visual field defect makes anatomical sense. There are a number of caveats, however:

— *Look for signs of an error in the OCT algorithm.* Errors are more likely when scanning a highly myopic eye because of the structural alterations associated with high myopia. For example, in the scan shown to the right, the thickness data is cut off at the top (blue arrow), leading to signal loss and an algorithm error. The nerve fiber layer thickness map pattern can still be used, but the quantitative values won't be accurate.

— *Make sure that any significant defects you see on OCT correspond with defects on the visual field.* For example, the patient we've been discussing has an inferior loss in the left eye and a superior arcuate bundle defect on the Humphrey 24-2 from the left visual field; there's a little arc that comes off the blind spot in that eye. That defect matches the anatomic nerve fiber layer loss on the OCT.

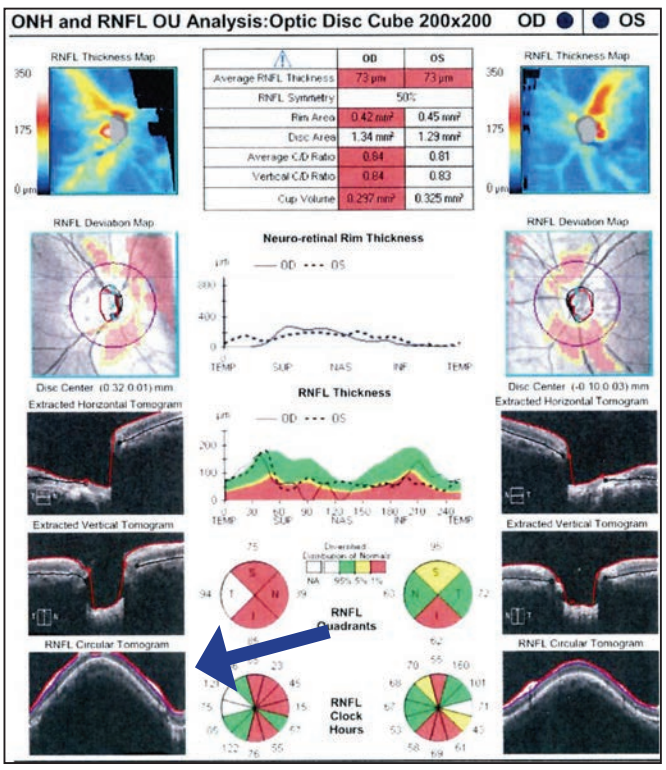
— *Beware of relying too much on the color codings of OCT results to indicate normal vs. abnormal.* It's best to compare each patient to his or her own baseline when looking for the smallest possible signs of change, rather than instrument analysis.

— *Remember that normative data does not account for whether individuals have high myopia.* That adds to the difficulty of following a high myope using OCT. For example, a 2012 study found that the superotemporal and inferotemporal RNFL bundles converge temporally with increasing myopia, which is associated with an increase in the area of abnormal RNFL measurement.[2] The authors concluded that interpreting a spectral-domain OCT RNFL thickness map in myopic eyes requires careful consideration of the distribution pattern of the RNFL bundles.

Another (retrospective) study published in 2016 found that when myopes with open-angle glaucoma had inferiorly tilted discs, they were likely to progress faster than those with a temporally tilted disc or non-myopic open-angle glaucoma, and they were more likely to have inferior visual field loss.[3] Again, this is not accounted for in normative data.

• ***Check the diurnal pressure.*** The appearance of normal IOP is one of the factors that makes these patients challenging to diagnose. Since the eye pressure reading is only a single measurement out of a continuum of IOP fluctuation, it's best to obtain multiple readings at different times of day; schedule some follow-up visits in the morning and some in the afternoon.

• ***Try to find pre-existing clinical data.*** Part of the reason this decision can be challenging is that you're working with data from a single point in time. Change caused by myopia is a result of expanding retinal defects and generally happens more slowly compared to change caused by glaucoma, so if there's any way to obtain clinical data from previous years, you can easily determine whether the abnormality you're seeing is long-standing or the result of worsening disease. If the old tests reveal the same defect with no change over years of time, you can be more confident that the abnormality is minimally progressive and



It's important to factor in OCT findings when judging how much vision the patient has left (a key factor in assessing the risk of waiting to see if progression occurs). However, look for signs of an error in the data, such as data being cut off (blue arrow). The nerve fiber layer thickness map can still be used, but the quantitative values won't be accurate.

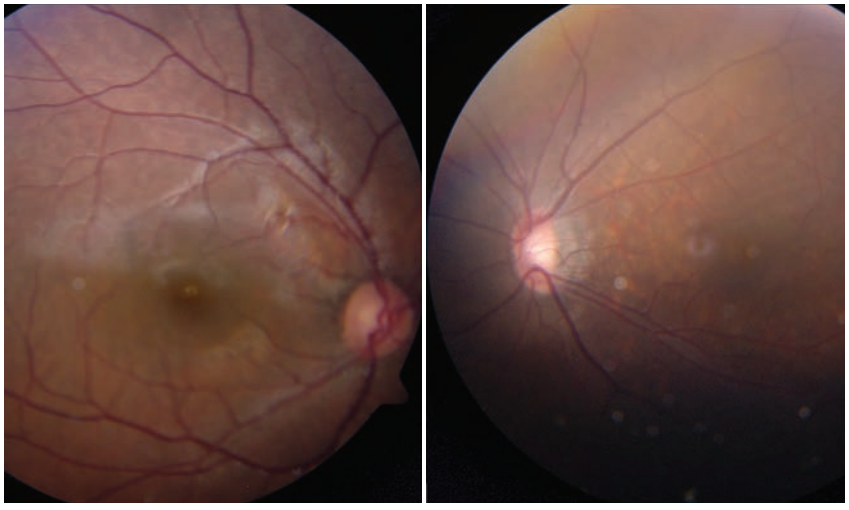
choose to observe without therapy. Unfortunately, we often don't have access to this kind of past data. However, that should become less of a problem with increasing electronic health record adoption.

• ***Focus on comparing the patient to himself or herself rather than the general population.*** Normative databases don't account for the effects of high myopia, so they can be misleading in these circumstances. The ideal way to determine whether a high myope has glaucoma is to compare multiple data points over time to see whether glaucomatous progression has been taking place. It's ideal to compare your data to previous images and fields, since the rate of change can be slow if the eye pressure isn't elevated.

For example, the images shown here *(above, right)* reveal what the optic nerves may look like in a pediatric patient who is extremely myopic. In this case, the patient's left eye is -11 D; his right was emmetropic. You can see that the left nerve is noticeably different in appearance. If you were to encounter this patient at age 40, having never seen this photo before, you might be worried that the left eye was glaucomatous. However, if you had access to this image of the nerve at age 11, you might conclude that the nerve looked pretty much the same back then, and you'd realize the patient was born this way. That's why this is so challenging; it can be hard to tell what's an anatomic abnormality and what is the result of progressive change.

• ***Find out what the patient is willing to do.*** Given the choices of eye drops or laser therapy, some patients may choose preventative therapy even if their true risk is low; others may only want treatment once the diagnosis is more certain. That's a discussion you need to have, to involve the patient in the treatment plan.

• ***Monitor the patient and look for change.*** If it's not obvious whether the patient has glaucoma or just high myopia, you can choose to monitor the patient, looking for the earliest confirmed deterioration in test results over time—hopefully, small enough not to affect visual function in daily life. This may be an acceptable choice, depending on the age of the patient, the patient's lifestyle and the amount of "reserve" tissue/vision that remains unaffected.



An 11-year-old high myope (-11 D OS). If you saw this patient at age 40, you might think he had glaucoma. However, if you had access to this childhood picture, you would probably conclude that his eyes had always looked like this, altering your diagnosis.

If you choose to monitor the patient, conducting serial testing using the same machine is key. You may want to do this on a more frequent basis at first, and then slowly space out the testing if no change is detected. In addition to following visual fields and OCT scans, be sure to monitor the optic nerve in comparison to baseline stereo disc photos; these have an advantage in that the technology doesn't change over decades (unlike OCT and visual fields).

Consider the Risk

When you have no definitive evidence to guide your clinical choices, the amount of risk associated with the choice to observe rather than treat is a key consideration.

• ***Consider how much vision reserve the patient has.*** How much vision does the patient have left to lose? Is the patient already symptomatic? Usually someone with large functional deficits is at higher risk, especially if the patient still has many years to live. In particular, a visual field index <40 starts to indicate low reserve.

• ***Consider how close the existing damage is to fixation.*** Damage that's already close to fixation puts the patient at greater risk, should the damage turn out to be caused by glaucoma. So, the closer the damage is to fixation, the more likely I am to treat, even if the patient has myopic retinal scars in the fovea that could also account for the field loss. (Usually the foveal threshold, if turned on during field testing, is depressed in early retinal disease relative to when it gets depressed in glaucoma.)

• ***If it appears to be glaucoma, consider how fast it's likely to progress.*** This plays a role when deciding whether to advance to a minimally invasive glaucoma procedure versus filtering surgery. In young high myopes, we often wonder whether

vascular risk factors play a role, leading us to seek out other treatable risk factors such as secondary causes, low blood pressure, migraines, sleep apnea, anemia, etc. One day there may also be a way to measure CSF pressure non-invasively.

Unfortunately, there's no published data telling us what exactly to do in any given anomalous optic disc situation, so most of us will probably start by making the more conservative choice. If the patient has a large defect with little vision in reserve, I'm more likely to initiate treatment because the patient can't risk any additional loss. On the other hand, if most of the eye testing still looks relatively normal—even with an abnormal-looking nerve—then I may choose to monitor for change to prove that glaucoma is the problem.

When You Might Want to Treat

If you're leaning toward treating for glaucoma, consider these factors:

• ***If the patient has a paracentral defect and a disc hemorrhage not due to other causes, I see this as a high-risk sign and tend to treat the patient.*** In an article in the March 2017 edition of *Review*, "Redfining Primary Open-angle Glaucoma," the author, Louis Pasquale, MD, discusses different possible subtypes of open-angle disease, including a type he calls PC-OAG, or paracentral open-angle glaucoma. These patients have a set of distinctive signs: a paracentral defect—more specifically, a triangular prelaminar neuronal defect within the cup that can be seen on OCT; a greater likelihood of disc hemorrhages; and a lower mean IOP than other glaucoma patients. They may also be younger than the average glaucoma patient, and are often described as normal-tension glaucoma patients.

As Dr. Pasquale notes—and my experience agrees—glaucoma patients fitting this description tend to progress rapidly, and they need lower-than-normal target pressures with multiple therapies to minimize progression. These are high-risk patients, regardless of being young and having normal pressures.

• ***If the cornea is very thin, or the patient has had previous LASIK, err on the side of treating for glaucoma.*** In either of these situations, it's more difficult to accurately monitor the patient's true eye pressure. That increases the risk of misjudging the patient's condition.

• ***Consider using a minimally invasive glaucoma surgery to treat a high myope.*** The well-known advantages of MIGS—being less risky for the patient and having fewer side effects compared to traditional filtering surgery, especially in high myopes—make a lot of sense when you're not certain whether the abnormality you're seeing is truly the result of glaucoma. If the disease is present, this approach could be sufficient to change the course of the disease, with less chance of a deleterious effect on the patient, even if the abnormality was caused by high myopia rather than glaucoma.

• ***Avoid going straight to filtering surgery.*** In most cases, at the initial visit you probably shouldn't recommend trabeculectomy to get the pressure into the single-digit range, unless you're certain the patient is high-risk based on historical data demonstrating clear worsening.

Moving Forward

The patient I described earlier initially agreed to use a single prostaglandin eye drop preventatively. While she was being treated, her intraocular pressure averaged between 12 and 14 mmHg, down from 18 mmHg. But after two years, she became pregnant and needed to go off the medication, and she declined to undergo selective laser trabeculoplasty. From that point on, we followed her with structural and functional tests but no treatment. The glaucoma-progression analysis over that five-year period on both OCT and visual fields indicated that there was no change in either eye, even after stopping treatment, and her pressures stayed in the mid- to high-teens range. Thus, it appears that her defects were due to high myopia rather than glaucoma.

The main point to remember is that myopic degeneration can cause the optic nerve to have an abnormal appearance, as well as produce field defects that mimic glaucoma. So before you automatically treat a high myope who appears to have glaucoma but doesn't have elevated eye pressure—especially before performing any kind of filtering surgery—take some of the steps described above. If the patient seems like a low-risk glaucoma suspect, it might make sense to follow the patient and see whether progression occurs. In higher-risk situations where treatment is called for, try lower-risk treatments initially such as drops, laser or MIGS surgeries. Only treat aggressively with filtering surgery if the patient has already lost substantial vision, or if you suspect the individual is potentially a fast progressor. REVIEW

Dr. Chang is an assistant professor of ophthalmology at the Byers Eye Institute, Stanford University School of Medicine. He's a consultant for Alcon, Allergan, Santen, Iridex, Pfizer, Aerie, Unity and Kali Care, and has received grant funding from Carl Zeiss.

1. Ding X, Chang RT, et al. Visual field defect classification in the Zhongshan Ophthalmic Center-Brien Holden Vision Institute High Myopia Registry Study. Br J Ophthalmol. 2016;100:12:1697-1702.
2. Leung CK, Yu M, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: Interpreting the RNFL maps in healthy myopic eyes. Invest Ophthalmol Vis Sci 2012;53:11:7194-200.
3. Han JC, Lee EJ, et al. Visual field progression pattern associated with optic disc tilt morphology in myopic open-angle glaucoma. Am J Ophthalmol 2016;169:33-45.

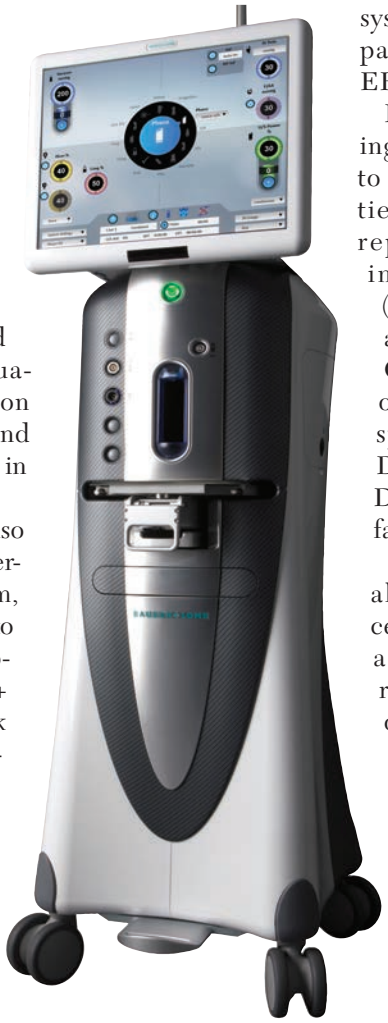
Equipment and Supplies / Career Opportunities

Practice For Sale

FDA Clearance for The Stellaris Elite

Bausch + Lomb's Stellaris Elite, the company's next-generation phacoemulsification platform, recently received 510(k) clearance from the U.S. Food and Drug Administration.

The company says that Stellaris Elite's Adaptive Fluidics system combines precise aspiration control and predictive infusion management and creates a highly responsive and controlled surgical environment for lens removal. The system is also designed to reduce IOP fluctuation and post-occlusion surge by monitoring and responding to changes in vacuum levels.



The Stellaris Elite also features the Attune energy-management system, using longitudinal cuts to complement the Adaptive Fluidics. Bausch + Lomb says these work together to deliver efficient, low-energy, controlled emulsification of the nuclear material.

For more information on Bausch + Lomb's Stellaris Elite, visit bausch.com.

First Insight Releases EyeClinic Imaging

In late March 2017, First Insight Corporation released EyeClinic Imaging, a cloud-based ophthalmic image management system that's compatible with most EHRs.

EyeClinic Imaging allows doctors to consolidate patient images and reports from all imaging devices (fundus cameras, visual fields, OCTs, etc.) into one management system through DICOM and non-DICOM interfaces.

Clinicians are also able to access data, images and diagnostic reports any time on any computer or mobile device, thanks to the cloud storage provided by the system. First Insight's new release also provides the ability to easily compare diagnostic images and reports side-by-side to detect changes and diagnose conditions.

Doctors are also able to share findings on-screen, helping patients understand their eye conditions and why certain tests are necessary.

For more information on First Insight's EyeClinic Imaging, visit first-insight.com/eyeclinic-imaging.

Alcon 2.5 D ReSTOR Toric Lens

In late March of 2017, Alcon received FDA approval for its new +2.5 D ReSTOR multifocal toric intraocular lens. This new lens is optimal for patients undergoing cataract surgery who wish to simultaneously address their astigmatism and presbyopia.

Alcon says that its new toric IOL is the only multifocal toric in which the central portion is 100 percent dedicated to distance vision, in contrast to previous presbyopia-correcting lens designs, which tended to compromise distance vision for a range of vision.

For more information on Alcon's new +2.5 D ReSTOR toric lens, visit myalcon.com.

Topcon's Aladdin HW 3.0 Biometer

Topcon recently announced the release of its Aladdin 3.0 Biometer. The device combines nine mea-

This article has no commercial sponsorship.

surements in a single instrument, allowing the surgeon to choose the spherical prescription of the IOL and the choice of the right premium IOL for patients.

The Aladdin combines the measurement of axial length, keratometry, anterior chamber depth, lens thickness, central corneal thickness, corneal topography, pupillometry and corneal diameter in a single instrument.

Topcon says some of the Aladdin's key features include the abilty to take all of the patient's necessary measurements in less than five seconds, and that the operator can print an IOL report with just three clicks. The biometer includes a built-in full Placido topography system that offers all the additional diagnostic capabilities of any standalone topographer. The Aladdin also comes equipped with an onboard Barrett IOL Calculation Suite, including the Barrett Rx, the Barrett Toric IOL Calculator, the Barrett True K and the Barrett Universal II formulae.

For more information on Topcon's Aladdin 3.0, visit topconmedical.com.

Precision Vision's Teller Acuity Cards

In late 2016, Precision Vision and the University of Washington agreed to become the main distributor and exclusive manufacturer of Teller Acuity Cards. These cards are a test of visual acuity for infants, young children and individuals with disabilities. Precision Vision says Teller Acuity Cards provide a solid foundation for ophthalmologists and optometrists to gather evidence on the visual acuity development of their pediatric or disabled patients. Although Precision Vision has manufactured these cards since 2011, the new agreement now makes them the sole manufacturer of Teller Acuity Cards.

All cards measure approximately 25.5 x 55.5 cm (10 x 22 inches). An instruction manual is included with each set. These cards allow for a multidistance, high-contrast test that provides a classic, straightforward measurement of infants' visual acuity.

For more information on Precision Vision's Teller Acuity Cards, visit precision-vision.com/product/teller-visual-acuity-16cards.

Stereo Optical's New Tests for Optec Plus

Newly announced by Stereo Optical, Optec Plus will now have a number of new tests that clinicians will be able to administer to patients. The Optec Plus is a smart-vision screener that now includes a more extensive library of tests in a single machine that are administered with a user-friendly interface.

Stereo Optical recently added a glare recovery test and the ability to administer its existing tests under the new glare conditions. It says that these tests are useful for quantifying vision loss under the glare conditions that can be brought about by the presence of cataracts or corneal scars.

Some features of Optec Plus include: thorough and repeatable results; testing near, far and intermediate distances; monocular and binocular testing; different lighting conditions (day and night); reverse background; constant and homogenous luminescence levels; light weight and portability; compatibility with both PC and tablets; wireless connectivity; quick and easy access to digital records; and no requirements for training or certification.

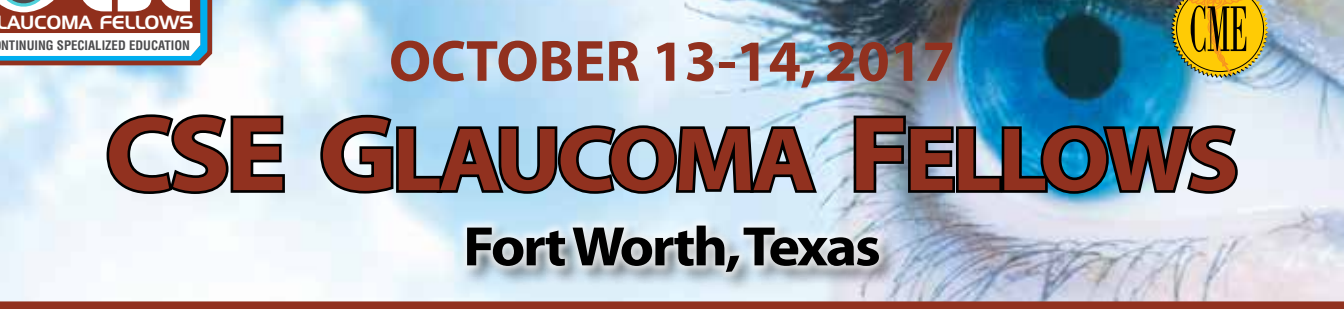
For more information on Optec Plus, visit stereooptical.com.

(Continued from page 48)

(anterior paracentesis, temporary tied sclerotomy or plugged [valved] trocar) to amputate any anterior posterior connection or, if it's a tiny strand, you can go in through another paracentesis, sharply cut the strand with scissors and push it back with some OVD.

"When removing viscoelastic after you've placed your IOL, it shouldn't be done aggressively, as this can cause re-presentation of vitreous, unless optic capture is achieved, sealing the posterior segment," Dr. Arbisser adds. "Miochol should be put in and a manual push/pull through the paracentesis performed. This is why I don't use Healon V in complex situations, because you can't leave it behind; but a little Viscoat left behind is more forgiving. In any case, it's a good idea to do some hypertensive prophylaxis, so I'll give a Diamox sequel if the patient isn't allergic to sulfa drugs. I'll also leave a little Triessence in the eye, placing it as a last maneuver to make sure no vitreous has come forward, as well as for its anti-inflammatory properties. Though it's off-label, I believe we should use intracameral antibiotics. I recommend moxifloxacin 150 µg/0.1 ml as suggested by Steve Arshinoff, MD. Also, when the patient's in the outpatient area, it's a good idea to administer one oral dose of Avelox (moxifloxacin 400 mg)—except in cases where the patient has an allergy to it." After surgery, she is aggressive with topical NSAIDs and a long steroid taper as an off-label cystoid macular edema prophylaxis. "A scleral indented exam is required, with timely referral to a vitreoretinal surgeon if there is residual nucleus," Dr. Arbisser says.

Looking back over the process, Dr. Reeves says, "An anterior vitrectomy in an unplanned setting is always an anxiety-provoking moment." However, he says that if you take your time, manage the anterior chamber well and carefully remove the vitreous, you can handle that moment successfully. REVIEW



ar Fellowship Program Director and Coordinator,

e would like to invite you to review the upcoming 2017 Glaucoma Fellowship Program Fort Worth at the Re-ssance Worthington hotel. The program offers a unique educational opportunity for fellows by providing the ance to meet and exchange ideas with some of the most respected thought leaders in glaucoma. The Glaucom llows Program is designed to provide your fellows with a state-of-the-art didactic and wet lab experience. The ogram also serves as an opportunity for your fellows to network with fellows from other programs.

er reviewing the material, it is our hope that you will select and encourage your fellows to attend this educa-nal activity which is CME accredited to ensure fair balance.

ncerely,
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Course Director:
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Email: dholmes@postgradhealthed.com or call Denette Holmes 866-627-0714

Participants in this course must be enrolled in a glaucoma fellowship program at the time of the course.
There is no registration fee for these activities. Air, ground transportation in Fort Worth, hotel accommodations and modest meals will be provided through an educational scholarship for qualified participants.

reditation Statement
activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for tinuing Medical Education (ACCME) through the joint providership of Amedco and Postgraduate Healthcare Education. Amedco is accredited by the ME to provide continuing medical education for physicians.

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activity has been approved for *AMA PRA Category 1 Credits*™.

Gradually worsening vision in both of his eyes brings a 41-year-old man to Wills Eye Hospital.

Martha Ryan, MD

Presentation

A 41-year-old Indian male presented with a four-month history of progressively blurry vision in both eyes. He initially noted decreased vision in his left eye at near and at distance, followed by similar changes in his right eye several weeks later. He also reported new floaters in both eyes. He denied associated headaches or eye pain, flashes of light, recent trauma or illness, and denied similar episodes in the past. He was first evaluated by an outside ophthalmologist, diagnosed with bilateral uveitis, and treated with topical corticosteroids and NSAIDs without improvement in his symptoms. He was also found to have cystoid macular edema that was treated with intravitreal injections of ranibizumab followed by aflibercept, with initial improvement followed by recurrence of the edema over the course of one to two weeks. Due to his refractory inflammation, he was referred to Wills Eye Hospital for further management.

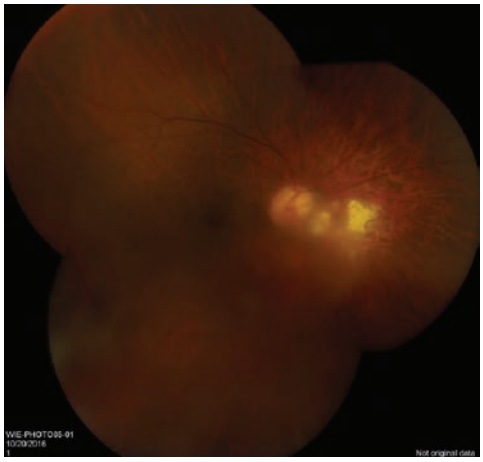

Figure 1. Fundus photograph of the right eye.

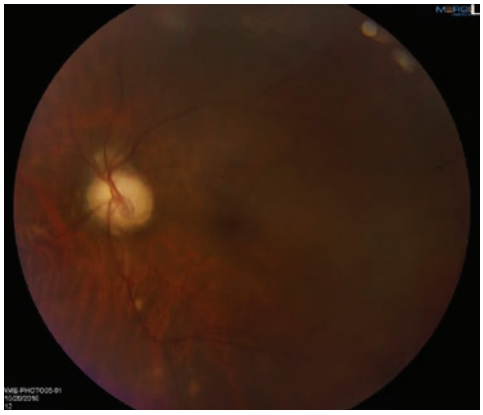

Figure 2. Fundus photograph of the left eye.

Medical History

Past ocular history was notable for glaucoma diagnosed 10 years earlier and controlled with dorzolamide 2%/timolol 0.5% and brimonidine 0.15%. He had no significant past medical history, and the review of systems was unrevealing. He took no systemic medications and had no known drug allergies. His family history was noncontributory. He denied tobacco and alcohol use. He had emigrated from Chennai, India, four years prior to his presentation.

Examination

Ocular examination demonstrated a best-corrected visual acuity of 20/40 OD and 20/50 OS. On pupillary exam there was no relative afferent pupillary defect, but the right pupil was noted to be sluggishly reactive. Extraocular motility was full in both eyes and visual fields were full to confrontation in both. The intraocular pressure was 9 mmHg OD and 12 mmHg OS.

On anterior slit lamp examination there was 3+ cells in the anterior chamber OD and 2+ cells in the anterior chamber OS. There were no keratic precipitates or synechiae. Funduscopic exam of the right eye *(See Figure 1)* demonstrated 2 to 3+ vitreous cells with moderate vitreous debris. The optic nerve was pink and healthy, the vessels were normal caliber without vasculitis and there was no macular edema. There was chorioretinal scarring nasal to the disc from 2 to 4 o'clock, and scattered snowballs were seen in the periphery. Fundoscopic examination of the left eye *(See Figure 2)* revealed 1+ vitreous cells with moderate vitreous debris and scattered snowballs. The optic nerve and vessels appeared normal, but there was macular thickening without retinal hemorrhage.

What is your differential diagnosis? What further workup would you pursue? Please turn to page 84.

Diagnosis and Workup

A diagnosis of bilateral panuveitis was made based on the history and ocular examination. The differential diagnosis at this time was broad and consisted of predominately infectious and inflammatory etiologies including: Lyme disease; syphilis; tuberculosis; toxoplasmosis; sarcoidosis; Vogt-Koyanagi-Harada syndrome; and white dot syndromes such as serpiginous chorioretinopathy. Further office-based testing was pursued. An OCT of the macula demonstrated cystoid macular edema in both eyes, the left greater than the right. On fluorescein angiography there was blocking over the peripapillary lesions with late hyperfluorescence of the lesion borders in the right eye. In the left eye, late leakage in the macula was noted. A-V transit time was normal. Systemic workup was also done, including chest X-ray, toxoplasmosis antibody, Lyme antibody, syphilis enzyme immunoassay and an interferon gamma releasing assay. All testing was within normal limits, except the interferon gamma releasing assay, which was positive. A diagnosis of ocular tuberculosis was made given our patient's clinical presentation and ocular exam, demographic risk factors and lab testing. He was referred to the health department and started on four-drug therapy per current guidelines.[1]

Discussion

Tuberculosis represents a massive burden to public health globally and it is a leading cause of morbidity and mortality worldwide.[2] The disease's prevalence varies, and the majority of tuberculosis cases occur in low- or middle-income countries. In 2012, there were more than 9,900 new tuberculosis cases reported in the United States.[3] While the majority of cases manifest as pulmonary tuberculosis, 16 percent of cases in the United States were extrapulmonary in one World Health Organization study of the disease.[2] In the United States, risk factors for tuberculosis infection include homelessness, imprisonment and emigration from or recent travel to an area of endemic disease. Of all cases of uveitis in this country, tuberculosis uveitis has an incidence of 0.5 percent.[4]

The pathogenesis of tuberculosis uveitis has not been fully elucidated by researchers. It is likely a manifestation of both primary active infection and secondary immune reaction to the latent *mycobacterium tuberculosis* organism. Primary ocular lesions are rare and are typically located on the conjunctiva, cornea or sclera. More often, ocular tuberculosis represents hematogenous spread of the mycobacteria from another site. For this reason, the highly vascularized uvea is most commonly affected.

The gold standard of diagnosis is isolation of the *M. tuberculosis* organism from ocular fluid or culture; however, this is rarely practical from a clinical standpoint. For this reason, it's typically a presumptive diagnosis. As suggested in a 2016 paper on the disease by Marcus Ang and his colleagues at the Singapore National Eye Centre,[5] a stepwise process is helpful in making the diagnosis.

Factors to support the diagnosis include the presence of ocular and systemic findings suggestive of tuberculosis infection, a positive interferon gamma release assay, a positive tuberculin skin test and improvement following anti-tuberculosis therapy.[5] However, in many reported cases of ocular tuberculosis in non-endemic areas, the eye was the only site of infection.[6] Ocular findings consistent with tuberculosis uveitis include a diverse array of pathology, but certain signs are more predictive of tuberculosis. In one study, India's Amod Gupta and co-workers found that the clinical signs most predictive of ocular tuberculosis were broad-based posterior synechiae and serpiginous-like choroiditis with or without vasculitis.[7] Consideration of these factors in a stepwise fashion can be used to aid in the diagnosis of ocular tuberculosis.

Tuberculosis skin testing and an interferon gamma releasing assay can also aid the diagnosis. However, there are no definitive guidelines on the use of these tests in the setting of uveitis, and there's wide variability in clinical practice. In a survey of members of the American Uveitis Society, 25 percent of respondents reported obtaining tuberculosis testing in all patients presenting with uveitis.[8] In a case similar to our patient, uveitis in a person with tuberculosis risk factors, 71 percent of respondents reported they would order a tuberculosis screening test.[8] In the same paper, 23 percent of those responding reported that they would treat a panuveitis patient with tuberculosis risk factors even if their tuberculosis screening tests were negative. This highlights the limitations of the currently available tests (interferon gamma releasing assay, tuberculin skin tests and chest X-ray).

Additionally, it is important to note that even though these tests may help make the diagnosis, they don't differentiate between active and latent infection. Furthermore, these tests' positive and negative predictive

values will vary widely given the dramatic variability in tuberculosis prevalence globally. While TB screening tests can be useful adjuncts, the importance of clinical correlation is especially critical in making this challenging diagnosis. The most typical presentations include "sticky" iridocyclitis, panuveitis, serpiginous-like choroiditis or chorioretinitis, choroidal tubercles and a choroidal mass; any of these findings with the appropriate history should raise suspicion of ocular tuberculosis.

While no formal treatment algorithm exists for ocular tuberculosis, most authors recommend six to 12 months of four-drug therapy for extrapulmonary tuberculosis.[9,10] From the previously mentioned survey of uveitis specialists, 26 percent of respondents reported they would treat a uveitis patient with TB risk factors for 12 months.[7] Concurrent corticosteroid therapy[9] or immunosuppressive therapy in steroid-intolerant patients[11] may be necessary to control any associated inflammation.

In summary, tuberculosis uveitis represents an uncommon entity in the United States but an important manifestation of a disease with a significant global burden. Proper diagnosis of tuberculosis uveitis presents multiple challenges, with no gold standard in most clinical settings. As in our patient, the absence of pulmonary or other systemic symptoms or findings of tuberculosis is common. While tuberculosis screening tests are valuable, there is significant variability in when and how these tests are used, even among uveitis specialists. Similarly, treatment is not standardized, and most providers rely on our infectious disease colleagues and Centers for Disease Control and Prevention guidelines on extrapulmonary tuberculosis to help guide their treatment. REVIEW

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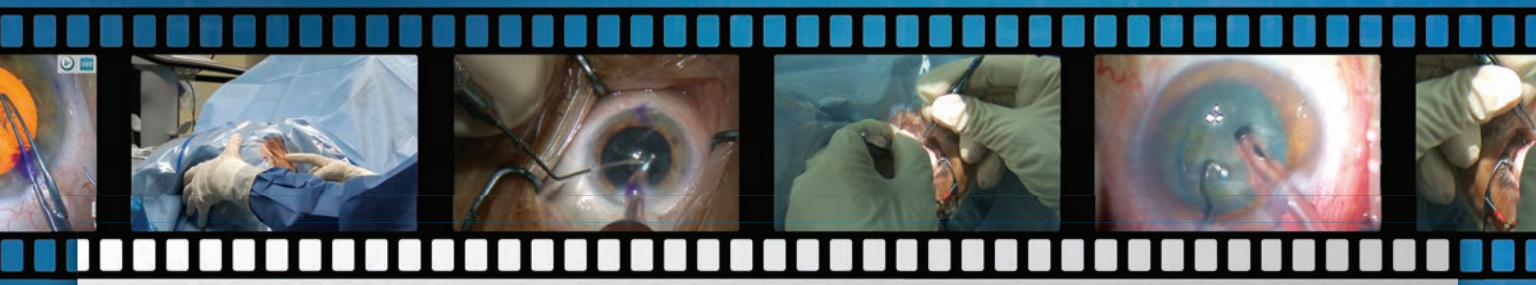

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Episode 17:
"The Photophobic and Hyperaesthetic Patient"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
Many patients experience severe photophobia in response to the microscope light. These patients are also often hyperesthetic, and this patient presented with both issues. Here I demonstrate the use of the "NLP" (no light perception) technique to eliminate photophobia, the soft lens/no ultrasound phaco method and the use of a low (50 mm Hg) IOP setting during phaco and I/A to eliminate the possibility of discomfort caused by a higher intraoperative IOP in this patient who also had a floppy iris.

MackoolOnlineCME.com MONTHLY Video Series

Richard J. Mackool, MD

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.

As before, one new surgical video will be released monthly, and physicians may earn CME credits or just observe the case. New viewers are able to obtain additional CME credit by reviewing previous videos that are located in our archives.

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

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:

- Apply methods to reduce photophobia and hyperaesthesia during phacoemulsification.

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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 Amedco and Postgraduate Healthcare Education, LLC (PHE). Amedco is accredited by the ACCME to provide continuing medical education for physicians.

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