Real-time DATA in the OR

Is Intraoperative Aberrometry Worth It? P. 21

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Cross-linking Approved, Now What? P. 36
**INDICATIONS AND USAGE:**

DUREZOL® Emulsion is a topical corticosteroid that is indicated for:
- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

**Dosage and Administration**

- For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.
- For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

**IMPORTANT SAFETY INFORMATION**

**Contraindications:** DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpetic simplex keratitis (dendritic keratitis), vaccinia, and variella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

**Warnings and Precautions**

- **Refractive increase** — 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.
- **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.
- **Infections** — Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

**Most Common Adverse Reactions**

- **Post Operative Ocular Inflammation and Pain** — Ocular adverse reactions occurring in 5-15% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.
- **Bacterial infections** — Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

**References:**

1. Durezol [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; May 2013. 2. Data on file. 3. Fingertip Formulary, October 2015 (estimate derived from information used under license from Fingertip Formulary, LLC, which expressly reserves all rights, including rights of copying, distribution and republication).
Topical Ophthalmic Use Only
DUREZOL® Emulsion is not indicated for intraocular administration.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to installation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

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

Ocular Surgery
Ocular adverse reactions occurring in 5-15% of subjects in clinical studies with DUREZOL® Emulsion included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cell, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in <1% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and irritis. Ocular adverse reactions occurring in >1% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and irritis. Ocular adverse reactions occurring in >1% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and irritis. Ocular adverse reactions occurring in >1% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and irritis. Ocular adverse reactions occurring in 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pain, pruritus, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions have been the consequence of the surgical procedure.

Endogenous Anterior Uveitis
A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 196 were exposed to DUREZOL® Emulsion. The most common adverse reactions of those exposed to DUREZOL® Emulsion occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, irritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2-5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects
Pregnancy Category C. Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal anomalies) when administered subcutaneously to rabbits during organogenesis at a dose of 10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to human exposure because of the species differences; other species, such as the female Chinese hamster. An in vivo micronucleus test in difluprednate in mice was also negative. Treatment of male and female rats with subcutaneous difluprednate up to 10 mcg/kg/day prior to and during mating did not impair fertility in either gender. Long term studies have not been conducted to evaluate the carcinogenic potential of difluprednate.

Animal Toxicology and/or Pharmacology
In multiple studies performed in rodents and non-rodents, subchronic and chronic toxicity tests of difluprednate showed systemic effects such as suppression of body weight gain; a decrease in lymphocyte count; atrophy of the lymphatic glands and adrenal gland; and for local effects, thinning of the skin; all of which were due to the pharmacologic action of the molecule and are well known glucocorticosteroid effects. Most, if not all of these effects were reversible after drug withdrawal. The NOEL for the subchronic and chronic toxicity tests were consistent between species and ranged from 1–2.5 mcg/kg/day.

PATIENT COUNSELING INFORMATION
Risk of Contamination
This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the emulsion. Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

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

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Patients should be advised to remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Released: May 2013
U.S. Patent 6,114,319

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Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Patients should be advised to remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Released: May 2013
U.S. Patent 6,114,319
Ranibizumab and aflibercept, used to treat vision loss from diabetic macular edema, and approximately 20 to 30 times more expensive than bevacizumab, are not cost-effective for treatment of DME compared to bevacizumab unless their prices decrease substantially, according to a study published online by *JAMA Ophthalmology*.

The anti-vascular endothelial growth factor drugs have revolutionized DME treatment. A recent randomized clinical trial comparing anti-VEGF agents for patients with decreased vision from DME found that at one year aflibercept (2 mg) achieved better visual outcomes than repackaged (compounded) bevacizumab (1.25 mg) or ranibizumab (0.3 mg); the worse the starting vision, the greater the treatment benefit with aflibercept.

These agents also vary substantially in cost. On the basis of 2015 costs, aflibercept was $1,850, ranibizumab, $1,170, and repackaged (compounded) bevacizumab, approximately $60 per dose. Considering that these medicines may be given nine to 11 times in the first year of treatment and, on average, 17 times during five years, total costs can be substantial. In 2010, when these intravitreous agents were being used predominantly for age-related macular degeneration, ophthalmologic use of VEGF therapy cost approximately $2 billion or one-sixth of the entire Medicare Part B drug budget. In 2013, Medicare Part B expenditures for aflibercept and ranibizumab alone totaled $2.5 billion.

Adam R. Glassman, of the Jaeb Center for Health Research, Tampa, Fla., and colleagues examined the incremental cost-effectiveness ratios (ICERs) of aflibercept, bevacizumab and ranibizumab for the treatment of DME with an analysis of efficacy, safety and resource utilization data at one-year follow-up from the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial. The researchers determined the ICERs for all trial participants and subgroups with baseline vision of approximate Snellen equivalent 20/32 to 20/40 and baseline vision of approximate Snellen equivalent 20/50 or worse. One-year trial data were used to calculate cost-effectiveness for one year for the three anti-VEGF agents; mathematical modeling was then used to project 10-year cost-effectiveness results.

The study included 624 participants; 209 in the aflibercept group, 207 in the bevacizumab group and 208 in the ranibizumab group. The researchers found that in eyes with visual acuities of 20/50 or worse because of DME, aflibercept produced greater average VA gains compared with bevacizumab or ranibizumab. The analysis suggested that the VA benefits of aflibercept translate into modest quality-of-life improvements, but at a high cost relative to bevacizumab, with the ICERs substantially higher than the thresholds per quality-adjusted life-year frequently cited in cost-effectiveness literature and U.S. guidelines. The authors add that it is unlikely that any realistic differences in VA achieved with the three agents during years two to 10 (in the range of changes seen in prior studies) would alter their relative cost-effectiveness.

In eyes with decreased vision from DME, treatment costs of aflibercept and ranibizumab would need to decrease by 69 percent and 80 percent, respectively, to reach a cost-effectiveness threshold of $100,000 per QALY compared with bevacizumab during a 10-year horizon.

"From a societal perspective, bevacizumab as first-line therapy for DME would confer the greatest value, along with substantial cost savings vs. the other agents. These results highlight the challenges that physicians, patients and policymakers face when safety and efficacy results are at odds with cost-effectiveness results," the researchers write.

**A1C Control Shows Major DR Benefit**

People with type 2 diabetes who intensively controlled their blood sugar...
level during the landmark Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial Eye Study were found to have cut their risk of diabetic retinopathy in half in a follow-up analysis conducted four years after stopping intensive therapy. Investigators who led the ACCORD Follow-on Eye Study (ACCORDION) announced the results at the American Diabetes Association annual meeting.

“This study sends a powerful message to people with type 2 diabetes who worry about losing vision,” said Emily Chew, MD, deputy director of the NEI Division of Epidemiology and Clinical Applications and lead author of the NEI-supported study, published online in Diabetes Care. “Well-controlled glycemia has a positive, measurable and lasting effect on eye health.”

ACCORDION is a follow-up assessment of diabetic retinopathy progression in 1,310 people who participated in ACCORD, which tested three treatment strategies to reduce the risk of cardiovascular disease among people with long-standing type 2 diabetes. ACCORD tested maintaining near-normal blood sugar levels (intensive glycemic control); improving blood lipid levels, such as lowering LDL cholesterol and triglycerides and raising HDL cholesterol; and lowering blood pressure.

The treatment phase of the glycemic control portion of ACCORD had been planned to last 5.6 years but was stopped at 3.5 years due to an increase in death among participants in the intensive glycemic control group. The blood pressure and blood lipid portions of ACCORD continued. Tight control successfully reduced glycemia to an average 6.4 percent A1C compared to 7.7 percent among participants on standard glycemic control therapy.

Although it failed to reduce cardiovascular disease risk, such
as heart attack and stroke, the researchers found that the therapy had cut retinopathy progression by about one-third by the end of ACCORD. Investigators considered progression to have occurred if a participant required laser surgery for diabetic retinopathy, required a vitrectomy or advanced three or more steps on the Early Treatment Diabetic Retinopathy Study Severity Scale. The scale uses photographs of the retina to rate disease severity from 1 (no disease) to 17 (high-risk for progression in both eyes).

ACCORDION re-assessed diabetic retinopathy about four years after the intensive glycemic control portion of the study had ended, eight years after enrollment in ACCORD. By then, average A1C was nearly the same: 7.8 percent for the intensive therapy group and 7.9 percent for the standard therapy group. However, diabetic retinopathy had advanced in only 5.8 percent of participants in the intensive therapy group since enrollment in ACCORD, compared to 12.7 percent in the standard therapy group.

Despite this equalization of glycemic control in the two groups, there continued to be an approximately 50-percent risk reduction of further retinopathy progression, a phenomenon termed metabolic memory,” said Frederick L. Ferris III, MD, NEI clinical director, who was not involved in the study.

Other clinical trials have reported the phenomenon, also known as the legacy effect. Participants with type 1 diabetes who received intensive glycemic therapy in the 10-year-long Diabetes Control and Complications Trial on average had 50-percent less progression of diabetic retinopathy three decades later. A similar trend was seen in the United Kingdom Prospective Diabetes Project, a study of people with newly diagnosed type 2 diabetes.

Results from ACCORDION suggest that lowering blood glucose can reduce progression of retinal disease relatively late in the course of type 2 diabetes and that even short-term changes in glucose can have an effect. The findings add to mounting evidence that tight glycemic control has positive, long-lasting effects on small blood vessels. Other follow-up studies of ACCORD participants have observed a legacy effect similar to ACCORDION in kidney and peripheral nerve health, which also involve small blood vessels. But the benefits of intensive glycemic therapy must be weighed against the potential risks—most notably the increased risk of death observed in ACCORD. Investigators have been unable to determine a cause for the increase, which was not seen in other trials.

Results also point to a possible role for ongoing use of fenofibrate to treat diabetic retinopathy, if taken regularly. The blood lipid and blood pressure portions of ACCORD concluded at 5.6 years. Neither strategy reduced cardiovascular disease. However, fenofibrate, a drug that raises HDL cholesterol, decreased diabetic retinopathy progression by about one-third during ACCORD. ACCORD investigators found fenofibrate had no lasting benefit three years after the drug was discontinued.

But based on ACCORD findings, fenofibrate might be worth taking to control diabetic retinopathy progression. Other countries, including Australia, have approved fenofibrate for treating diabetic retinopathy but not the United States, said Dr. Chew. The NEI-funded Diabetic Retinopathy Clinical Research Network is currently planning a clinical trial to further explore ongoing use of fenofibrate to control diabetic retinopathy.
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Thanks and Farewell

Mark H. Blecher, MD
Chief Medical Editor

It’s been many years since I’ve appeared in these pages, where I once monthly opined on the state of private practice in ophthalmology. I resisted the calls over the years to again share my thoughts, as I didn’t feel there was anything sufficiently important compelling my return. I was wrong. I return to bring attention to a true milestone that shouldn’t go unnoticed. This issue marks the final Review of Ophthalmology under the editorial guidance of Chris Glenn. Chris is making the enviable transition to retirement, putting aside fonts and files for a life of leisure and music.

Review was founded to inhabit a unique niche in medical publishing. Positioned between peer-reviewed journals overloaded with information both interesting and obscure, and “throw-aways” crammed with practical, industry-driven articles, Review strove to bring to ophthalmologists an impartial distillation of what was clinically useful and academically important. In this model, the role of the editor was paramount. Along with myself, our section editors, and the magazine’s entire editorial board, Chris was responsible for bringing the best of ophthalmology, without bias, to your desk every month.

Chris has spent most of his journalistic career in eye care, moving from Review of Optometry to Review of Ophthalmology in 1999. He took his role as defender of the gates of journalistic integrity very seriously. In this age of dollar-driven relevance, he fought hard to keep outside influences and physician egos from corrupting the stories that we would tell.

So, as Chris readies for the post-work world, I personally want to thank him for his leadership, his dry humor, his Don Quixote complex and his friendship. And if any of you find yourself in the Philadelphia area, and you come across Chris strumming away on his guitar at an appropriately authentic Irish pub, be sure to buy him a Guinness.

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IMPORTANT SAFETY INFORMATION

OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% must be added to irrigation solution prior to intraocular use.

OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients. Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation. Use of OMIDRIA in children has not been established.

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.


Please see the Full Prescribing Information at www.omidria.com/prescribinginformation.

*Individual insurance coverage and policies may vary, and Omeros does not guarantee insurance coverage or payment. Omeros offers payments under the OMIDRIAssure “We Pay the Difference” program on behalf of qualifying patients. OMIDRIAssure is subject to change without notice.
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**INDICATIONS AND USAGE**

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

**IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®**

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

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

**References:**
1. PROLENSA Prescribing Information, April 2013.

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

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

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

CONTRAINdications
None

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

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

Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. These events may be increased 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 conjunctival 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.

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, ocular hypertension, 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.

Advising patients that a single bottle of PROLENSA® ophthalmic solution, be used to treat only one eye.

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

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

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New Apps for Billing, Surgery and Education

Digital platforms designed to help doctors and their patients continue to expand their capabilities and the areas they cover.

Christopher Kent, Senior Editor

As digital platforms become ubiquitous and increase in speed and capability, new applications designed to help ophthalmologists manage their work continue to proliferate. Here, app creators share the latest developments in two existing apps and one that should soon be available.

Help With Billing

One app many ophthalmologists may find useful is OphthoBilling (currently available at the Apple App Store). OphthoBilling was developed in 2015 by Renelle Lim, MD, during her fellowship training on the Oncology Service at Wills Eye Hospital in Philadelphia. “Traditional coding resources involve a computer or multi-volume book sets,” she says. “I wanted to create something that makes this information more readily available.”

Dr. Lim explains that the OphthoBilling app helps the user select both CPT (procedural) and ICD-10 (diagnosis) codes. “You can type in a keyword, type in the numerical code or just scroll to find the available codes,” she explains. “The app will tell you which codes can be used together and which cannot. OphthoBilling is especially helpful for the physician in the operating room or a surgeon who operates at multiple locations.”

Dr. Lim says the app has a straightforward interface and is very user-friendly. “It takes the guesswork out of billing and should reduce the number of errors and rejections from insurance companies,” she says. “The app can be a valuable tool for both ophthalmologists and billing assistants. It encourages physicians to take a more hands-on approach to billing, and it offers surgeons the opportunity to refine a final list of codes that accurately reflects the procedures performed during surgery, since only the surgeon knows the intricate details of each operation.” (See examples, facing page.)

“Once all CPT and ICD-10 codes are entered into a list within the OphthoBilling app, it can be texted, air-printed or e-mailed,” she adds. “The app creates an automatically tabulated list and displays the relative value units, giving the user an indication of reimbursement. Each surgeon can also create customized lists of codes based on the scope of the practice.”

Dr. Lim says the OphthoBilling app is currently available on the App Store for $99.99. You can view an introductory video online at https://www.youtube.com/watch?v=gGffMvjfHWk.

Managing Surgical Data

Anil Shivaram, MD, a cataract and refractive surgeon in Claremont, Calif., is part of a team working with Bausch + Lomb, IBM and Apple to create a multipurpose app that will help cataract surgeons manage surgery-related data in multiple ways. “This app is intended to help optimize outcomes in cataract surgery by capturing and organizing preoperative data and making it available to the surgeon in the OR,” he says. “Even more exciting, it will also capture postoperative data and analyze all of it to help the surgeon refine constants, lens selection and surgical choices.”

“Preoperatively, we do a number of tests to collect data such as axial length, keratometry and OCT scans,” Dr. Shivaram notes. “This is often done in a piecemeal way using different manufacturers’ instruments. Collecting, ensuring the accuracy and...
organizing the data can be messy, and having access to it in the operating room may involve—for some surgeons at least—having a lot of sticky tags or printouts taped to the wall. With this app, the surgeon will be able to simply take a photograph of each printout, on-screen test result or scan. Image recognition software will pull out and organize the numbers while saving images such as scans and topographies. This will reduce transcription errors and pool all of a patient’s data in one place that can be digitally accessed in the OR, something like a digital tablet. That information can also be easily accessed later if you’re doing the patient’s second eye, for example. The app will show you the result of the first eye’s surgery, to help you decide what you want to do with the second eye.”

Dr. Shivaram acknowledges that optical character recognition could potentially introduce errors, at least compared to a direct digital transfer of data. “We’re conducting a pilot study to determine the level of accuracy of this approach,” he says. “The advantage of having optical character recognition functionality is that there are a variety of machines out there being used by surgeons. This app will allow you to collect the data from any instrument without the need for an additional electronic tool or hookup. The app will also allow the surgeon to make manual changes to the data because sometimes, even with the correct data captured, a surgeon may wish to make adjustments.”

Dr. Shivaram notes that some surgeons take the time to analyze all of their data in order to refine their technique and generate better outcomes. “Since I was a resident I’ve been keeping an Excel spreadsheet tracking every single case I’ve ever done,” he says. “It’s become rather massive. It enables me to see exactly how my choices affect my outcomes with each lens I use, but doing this manually can take a lot of time and effort. If you have an app that integrates all of this data and analyzes it for you, you can optimize your outcomes without having to do the regression analysis on your own.

“For example, at postoperative visits, the data will compare the current measurements to your preoperative prediction,” he continues. “You’ve told it which lens you used, your preferred incision location and so forth. Over time it will refine your constants based on this information and make suggestions to reduce astigmatism and refine your outcomes. That’s a big deal, because many surgeons just use a standard A-constant and never refine it. Customizing those factors based on your individual results could go a long way toward improving your results, but it’s a tall order if you don’t have a meaningful way of accessing and crunching and analyzing the numbers. Given the serious computing power these companies bring to the table, the app can easily do a large, pooled analysis to help determine things like the effective lens position for different lenses and the relative importance of lens thickness or anterior chamber depth.

“At the end of the day, we really want to get LASIK-like outcomes with our cataract surgery,” he notes. “Patients, especially in the age of refractive surgery, are expecting results closer to your target. Using a data-driven process like this pushes us closer to being able to achieve that.”

Dr. Shivaram says the team will be conducting the aforementioned pilot study starting before the end of the year. “The study will test a number of things,” he says. “First, it will see how valid the software’s recommendations are, using a pool of data we’re collecting. For example, is it successfully optimizing each surgeon’s constants? Second, it will compare the efficiency of using the app versus not using it. How much more efficient are you when you have all of this data in one location? Does it save time in the OR? Third, we’ll see whether the app is reducing data input error.

“In the future, we plan to fully utilize the functions of the Apple devices and the security and cognitive computing power of the IBM Cloud services,” he adds. “This app will be the framework on which more ophthalm-
mic services can be deployed. It will take a number of processes that are onerous and time-consuming for the surgeon and make them a lot easier and less error-prone.”

Alexander Faust, an associate partner at Global Business Services—a subsidiary of IBM—who is also working on the project, says IBM is excited to be working with Dr. Shivaram, along with a select group of opinion-leading surgeons and the Bausch + Lomb team. “Our goal,” he says, “is to collaborate with these medical professionals to drive an enhanced quality of patient surgical eye care by delivering a mobile, digital transformation in ophthalmology.”

Andy Chang, senior vice president and general manager, U.S. Surgical, Bausch + Lomb agrees. “Working in collaboration with industry experts IBM and Apple, our goal is to help simplify a cataract surgeon’s ability to achieve target refractive outcomes by providing more intelligent recommendations through the mobile integration of diagnostic data and information,” he says. “Combining the diagnostics in one place and delivering personalized IOL recommendations that fit each individual will ultimately help surgeons make better, more-informed decisions for their patients; it will also increase efficiency by reducing the time needed for data transfer and manual computing, as well as limiting the risk of human error.”

A prototype of the app should be completed by the end of the year.

CheckedUp Adds New Content

CheckedUp is a customizable digital platform that allows doctors to give patients access to information about their condition and treatment—before or after seeing the doctor—at home via smartphone, computer or tablet, or in-clinic via kiosks. Originally focused on cataract surgery, the program has recently added multiple new topics and has also increased its functionality.

As before, all content is interactive; the platform provides information to the patient and allows the patient to provide feedback that’s forwarded to the doctor prior to the office visit. The material patients can access can be customized for each surgeon, so patients see exactly what the doctor wants them to see, and the content is constantly being upgraded based on feedback from practices. CheckedUp also includes a follow-up component; it provides data metrics to the practice showing how the program is doing at engaging and educating the patient and how adherent the patient is.

“We’ve recently added a dry-eye platform,” says Richard M. Awdeh, MD, assistant professor of clinical ophthalmology and assistant professor of ophthalmology and pathology at the Bascom Palmer Eye Institute in Miami, creator of the CheckedUp platform. “In addition to answering patient questions, it can help prequalify patients for any premium practice offerings, such as diagnostic tools or types of treatment. CheckedUp also now has educational material for patients diagnosed with many ophthalmic conditions such as glaucoma, macular degeneration or blepharitis, and for patients interested in procedures such as LASIK.”

Dr. Awdeh notes that getting information from the patient outside the office can result in a higher-quality consultation. “The doctor can see which content the patient looked at and the answers the patient gave to the questions before the patient is in the examination room,” he says. “Doctors and other staff members are already informed about the patient’s questions, objectives, concerns, level of education regarding the topic and any symptoms the patient may be experiencing. Meanwhile, being able to access the appropriate information outside the office means patients can refer back to the content at any time, and they’re able to share it with family and friends.”

Dr. Shivaram is a consultant for Bausch + Lomb. Dr. Awdeh has a financial interest in CheckedUp.
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. Intracocular inflammation has been reported with the use of EYLEA.
- Acute increases in intracocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intracocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intracocular 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 1.6% (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 is a registered trademark of Regeneron Pharmaceuticals, Inc.

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777 Old Saw Mill River Road, Tarrytown, NY 10591

Choose EYLEA® (aflibercept) Injection from the start

Learn about EYLEA at EYLEA.us/rt

As demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in patients with DME
5.2 Increase in Intraocular Pressure.

Intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

5.3 Thromboembolic Events.

The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (102 of 5786) in the combined group of patients treated with EYLEA. The incidence in the DME studies baseline to week 52 was 3.3% (19 of 578) in the group of patients treated with EYLEA combined with 2.8% (out of 281) in the control group: from baseline to week 100, the incidence was 6.4% (37 of 578) in the combined group of patients treated with EYLEA compared with 4.2% (out of 281) in the control group. There were no reported thromboplastic events in the patients treated with EYLEA in the first six months of the RIVO studies.

Uncommon adverse reactions reported in <1% of the patients treated with EYLEA are:

- Cataract
- Conjunctival hemorrhage
- Conjunctivitis
- Corneal epithelium defect
- Corneal edema
- Corneal ulcer
- Corneal edema or ulcer
- Corneal edema, pannus
- Injection site pain
- Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, iris, eyelid and entropion.

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 intraocular 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.

6.2 Immunogenicity.

In the wet AMD and RVO, DME studies, the pre-treatment incidence of antibodies to EYLEA was approximately 4% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8. USE IN SPECIFIC POPULATIONS.

8.1 Pregnancy.

Pregnancy Category C. Albireft may produce embryofetal toxicity when administered during the three days following 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, ectodactyly, intracranial atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternal cleft, and rib, supernumerary vertebral arches and ribs, and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) was 3 mg per kg. Albireft 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 exposures (AUC) that was approximately 10 times the systemic exposure observed in humans on an intravitreal exposure 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.

8.3 Nursing Mothers.

It is unknown whether Albireft is excreted in human milk. Many breastfed infants are exposed to human milk, a risk to the mother and a risk to the breastfed infant. Albireft 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 has not been established.

8.5 Geriatric Use.

In the clinical studies, approximately 76% (204/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1225/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age.

17 PATIENT COUNSELING INFORMATION.

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachments (see Adverse Reactions). Proper aseptic technique and treatment of a single eye. If the contralateral eye requires treatment, a new va

The nearby text is a part of the previously extracted text. The extracted text is: **Table 2: Most Common Adverse Reactions (%) in RIVO Studies**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EYLEA (N=218)</th>
<th>Control (N=142)</th>
<th>EYLEA (N=201)</th>
<th>Control (N=138)</th>
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<td>conjunctival hemorrhage</td>
<td>12%</td>
<td>3%</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>corneal edema</td>
<td>8%</td>
<td>2%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>corneal ulcer</td>
<td>1%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>injection site pain</td>
<td>1%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
| Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, iris, eyelid and entropion.
As every cataract surgeon knows, patient expectations for LASIK-like outcomes continue to rise. One of the technologies that has the potential to nudge cataract surgery outcomes closer to perfect is intraoperative aberrometry, which measures the patient’s refraction on the table during surgery. The ORA system with VerilEye+ technology (currently available from Alcon)—formerly Orange—has now been in use for a number of years; it has recently been joined in the United States by the HOLOS system from Clarity Medical.

Here, surgeons familiar with both systems talk about the current status of the HOLOS system, the ways in which ORA and HOLOS differ and why they believe surgeons should seriously consider adding this type of technology to their cataract surgery armamentarium.

**HOLOS: A New Formula**

Barry Linder, MD, chief medical officer at Clarity Medical Systems, explains that the HOLOS IntraOp system is currently in limited release in the United States. Its capabilities right now include monitoring real-time refraction throughout surgery, confirmation of hitting a target refraction and the ability to neutralize cylinder in pseudophakia with a toric lens and/or titrate limbal relaxing incisions at any point in the surgery. One of the key functions of intraoperative aberrometry—using the aphakic refraction to predict a spherical lens power—is currently being finalized and should become part of the system by late summer.

“We’re still collecting the data that our external consultants—including Doug Koch, Warren Hill and Graham Barrett—are using to finalize the development of our IOL algorithm,” explains Dr. Linder. “Dr. Barrett is doing much of the heavy lifting, with the Barrett Universal II and Rx formulas as the starting point. The resulting formula will be called the HOLOS-Barrett IOL formula. We’re making terrific progress; we have the basic outline of the algorithm and we’re integrating it into our software. The new version of the HOLOS software will also include new database management tools, such as a cloud-based physician portal for preoperative data input and connectivity to the HOLOS device in the OR via the cloud.”

Warren E. Hill, MD, FACS, medical director of East Valley Ophthalmology in Mesa, Ariz., is one of the experts helping to collect data and finalize the formula that will become...
Experts say that many surgeons don’t carefully evaluate their outcomes, often assuming their results are better than they actually are. Warren Hill, MD, assembled this data from more than 260,000 optical biometry cases submitted for Haigis formula optimization from 2004 to 2015. Less than 1 percent of surgeons consistently got 90 percent of patients to within 0.5 D of target; most surgeons only had 59 to 78 percent fall within that range.

part of the HOLOS system in the next few months. “The formula will take the vergence of the aphakic eye and convert it into an IOL power for the doctor to use at the time of surgery,” he explains. He notes that this type of formula is important because the pseudophakic spherical power measurement taken after lens implantation may not be as accurate as a formula’s prediction. “The pseudophakic confirmation is good to have,” he says, “but most surgeons who use intraoperative aberrometry depend more on the aphakic reading and the IOL power recommendation made by the instrument.”

“The issue here is that the power of the lens inside the eye is relative and not absolute,” he continues. “A 21-D lens is only 21 D at one specific distance from the cornea. When you’ve just put the lens inside the eye, its position has not yet been finalized by capsular bag contraction. In the pseudophakic state this technology is outstanding for seeing whether the corneal astigmatism has been corrected, but it may be less useful as an immediate means to check the spherical power. On the other hand, surgeons often change their original lens choice up or down 0.5 D based on the aphakic measurements and formula’s lens suggestion.”

**HOLOS Features**

In addition to implementing the new formula, the designers of the HOLOS system are working to incorporate features that will help it compete with the ORA. Those features include:

- **A new aberrometer.** “One advantage of the HOLOS instrument is that its aberrometer is a technologically advanced device that was designed specifically for this purpose,” notes Dr. Hill. “The ORA uses a Talbot moiré aberrometer, technology from the 1980s that was developed for a different purpose. The HOLOS aberrometer is very fast and very accurate, and the data is continuously filtered through measurement qualifiers. That means that before a measurement is displayed on the screen it has to pass muster, so to speak. As a result, the HOLOS aberrometer is accurate within 0.25 D at the corneal plane, with a 40-D dynamic range. And because the data is continuously displayed, a separate person is not needed in the OR to operate the system.”

- **Data presentation.** Dr. Linder says the forthcoming upgrade will include significant updates to the graphical user interface on the device, for use in the OR. “The HOLOS system will present the data in a unique way,” he says. “Current users of intraoperative aberrometry capture several ‘snapshot’ readings before making an IOL power selection, in order to feel confident that the measurements are accurate. This can take several minutes to accomplish. The HOLOS system constantly takes about 90 readings per second and qualifies each one so that it makes its IOL calculations using only readings that are qualified. And instead of showing the result of snapshots taken by the surgeon, the HOLOS will display a frequency histogram that shows, in real time, what percentage of the time a particular IOL power is recommended by the formula. (See sample screenshot, facing page.) It will be easy to see which IOL power is supported by most of the readings. This is a very different way to manage this information. It’s intuitive, easy to use and much faster than stopping and taking snapshots of periodic readings.”

- **No need to refocus.** Dr. Linder notes that the instrument’s focus doesn’t need to be changed as the microscope is adjusted. “The ORA system requires periodic refocusing,” he says. “With HOLOS, the focal point is kept at the iris plane or wherever the surgeon is operating. The data is always being generated and qualified, and the surgeon doesn’t have to re-adjust the scope to get the qualified readings. It’s one less thing for the surgeon to think about.”

Keith Liang, MD, medical director of the Sacramento Eye Surgery Center in Calif., says he’s been using the HOLOS system since Clarity began developing it; he’s currently providing data to help with the development of the new IOL power formula that will soon be incorporated into the system. He says he likes not having to refocus the HOLOS when the microscope is adjusted. “You don’t have to change the focus or turn off the microscope light and elevate the system to a certain height above the cornea to obtain...
a reading, like you do with ORA," he says. "With the HOLOS system, the focus corresponds to your focus in the microscope. That helps your OR efficiency."

- **Improved light visibility through the optics.** Dr. Linder says the optics in the HOLOS system are designed to take less light away from the optical path in the microscope than the ORA does. Dr. Liang says he has noticed the difference. "Both instruments go under the microscope, but with HOLOS the image coming through the oculars remains bright," he says. "When you put the ORA system underneath the microscope, it reduces the light coming through the oculars noticeably. You can counteract that by increasing the intensity of the light, but sometimes that's uncomfortable for the patient. For the surgeon it's very ergonomic to keep the lighting the same."

**Advantages of ORA**

P. Dee G. Stephenson, MD, current president of the American College of Eye Surgeons and an associate professor of ophthalmology at the University of South Florida College of Medicine in Tampa, has been using the ORA system for many years; she was the first commercial user of the system in the United States. "ORA has 500,000 cases in its AnalyzOR databank," she notes. "There are many different lens model outcomes that have been optimized in ORA, so it will be a long time before HOLOS has the experience that ORA has. ORA paved the way in intraoperative aberrometry, and every upgrade they've made has been an improvement."

"There are some great minds working on the HOLOS system," she acknowledges, "but when you come out of the gate, you're not going to be perfect. It's taken ORA more than seven years to get where it is, and it works amazingly well. In particular, it has become very accurate with most post-refractive patients, and it's getting better with post-RK and post-hyperopic LASIK patients."

Dr. Linder notes that while the HO-
LOS system will not initially have the advantage of incorporating data from thousands of cases, as the ORA system currently does, it won’t be starting from zero. “Our formula will be based upon the Barrett Universal II and Rx formulas,” he points out. “These formulas are well-understood and validated; they are considered to be some of the most accurate in the world. So we’re not starting from scratch; we’re building upon very well-accepted and validated IOL algorithms.

“In addition, the team that’s developing this has an extraordinary amount of experience,” he continues. “For example, Warren Hill has more than a quarter million cases that can be used to adjust constants based on factors such as design, materials, haptic/optic junction angulation and stability in the eye. So although we won’t have a huge database of cases at the outset, we have the foundation of a validated formula developed by surgeons with some of the most advanced knowledge available regarding how to optimize constants for the variety of IOLs that a surgeon might use.”

Dr. Stephenson agrees that the two Barrett formulas used as the basis for the HOLOS predictive formula are well-established and accepted, but notes that the ORA uses multiple leading formulas, including the SRK/T and Holladay I. “The ORA system uses a modified version of the refractive vergence formula, which incorporates the measured aphakic spherical equivalent,” she says. “It also analyzes regression coefficients—every lens model has a unique set of them—and the surgeon’s factor. Those data are refined and optimized globally and quarterly, incorporating the postoperative refractive data you enter. When you use it for the very first time, your information will be compared to global data. Over time, the system personalizes your own surgeon factor.”

Those working on the HOLOS system often point out that it captures data in real time, citing this as an advantage over the ORA. Dr. Stephenson takes issue with that. “I know HOLOS says it’s real-time, but so is ORA,” she says. “There’s a streaming refraction on the top of the screen, and as you move the eye, that changes. When you take a reading, you’re capturing one moment in time, but you see the changes occurring in real time.”

Dr. Linder acknowledges that ORA users also see refractive data changing in real time during surgery, but still says there are differences. “The frequency of the data collection and how it’s processed and displayed is significantly different,” he says. “Our data is being processed and qualified 90 times a second, and all of the qualified data points will be fed through the predictive algorithm. The on-screen histogram display will show which prediction is being supported the most by the ongoing data, which could include hundreds or thousands of measurements, depending on how many seconds the surgeon chooses to hold the eye under the device during aphakia. So the process will be very fast and intuitive, leading to the surgeon having a high level of confidence in the prediction.”

Is the Tech Worth the Cost?

As is often the case, adding new technology like intraoperative aberrometry can be an expensive proposition. Nevertheless, many surgeons see it as a worthwhile investment. “All surgeons pride themselves on great outcomes,” Dr. Stephenson points out. “If you ask your colleagues about their outcomes, most people will say they’re within 0.5 D of their intended target. But if you look at the real world, only between 70 and 80 percent of surgeons actually are.” In reality, most surgeons only guessimate what their surgically induced astigmatism is in
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Keith Liang, MD, medical director of the Sacramento Eye Surgery Center, notes that one of the things that makes data produced by intraoperative aberrometry different from preoperative data and calculations is that intraoperative aberrometry is entirely measured by the surgeon. “When you’re taking the measurement in the OR, it’s you, the surgeon, who dictates the accuracy of the reading,” he says. “In your preoperative calculations, you’re rarely the person running the instruments and taking the measurements. Obviously you oversee the preoperative measurement process and train your staff well, and there are things that can help you determine whether the preoperative readings are good or not. But you can’t take the readings yourself in a busy clinic. In contrast, you have complete control when you take a reading with intraoperative aberrometry.”

P. Dee G. Stephenson, MD, current president of the American College of Eye Surgeons and an associate professor of ophthalmology at the University of South Florida College of Medicine in Tampa, a long-time user of the ORA system, notes that if you want to get accurate information using intraoperative aberrometry, managing the details matters. “You have to follow a cookbook recipe to use this technology, but if you follow it, it really works,” she says. “You have to keep the cornea clear. You have to get all of the viscoelastic out of the cul-de-sac. You can’t have pressure on the eye from the lid speculum. You can’t just guesstimate the intraocular pressure by feeling the eye; you have to measure it with the Barraquer tonometer, and it has to be about 20 mmHg. You can do final readings with either BSS or viscoelastic in the eye, but it can only be one type of viscoelastic; you can’t have two kinds in the eye when you take the reading.”

Dr. Liang notes that this is all on the surgeon. “When you’re in the OR with the HOLOS or ORA, you can’t blame anyone else for not lining up the eye, not getting the pressure right or not irrigating the surface,” he says. “It’s all up to you. Maybe your preoperative calculations are great and the system will confirm them time after time. Maybe, after analysis, you’ll find that the intraoperative aberrometry data is better, and you can then work to find out why that’s the case and improve your preoperative measurements or calculations. Either way, you should end up generating better outcomes.”

—OK

each eye. They never actually calculate it. The problem is, to get great outcomes, you have to know those things.”

Dr. Stephenson says that she’s had great results using intraoperative aberrometry. “I just published data from 150 cases that are two years out, all done using ORA,” she says. “About 92 percent of these patients have 0.5 D or less of residual cylinder, and about 86 percent have 0.25 D or less. When addressing astigmatism, I don’t even mark my patients any longer. I go by what ORA tells me.”

Dr. Hill agrees that doctors who are skeptical of the value of this kind of technology usually aren’t tracking their outcomes. “Very few people do, and most surgeons think they’re getting much better results than they actually are,” he says. “The vast majority of ophthalmologists have ±0.50-D accuracy in the mid- to high-70 percent range. Intraoperative aberrometry will typically move most surgeons into the mid- to high-80 percent range. Of course, because we haven’t finalized the formula for HOLOS, this is ORA data.”

Dr. Liang says that whether or not intraoperative aberrometry is worth the cost for a given practice depends on several factors. “For one thing, the more surgeons you have in your practice or surgery center, the lower the cost will be,” he says. “It also depends on how many premium lenses you’re doing, because for those patients it’s especially important to deliver what you’re promising. Furthermore, the more confident you are that you can deliver on your promised outcome, the more you’ll offer the premium lenses.

“For example,” he continues, “at the last Ophthalmology Innovation Summit meeting a survey suggested that only 7 or 8 percent of IOLs being implanted were toric IOLs; meanwhile, more than 65 percent of patients getting cataract surgery have significant astigmatism that could be corrected. Another poll found that most doctors don’t believe that a toric lens rotation of 10 degrees or less is significant in terms of patient satisfaction. That’s a dangerous assumption to make. In any case, intraoperative aberrometry definitely improves toric lens power selection and alignment, although it takes a little extra time in the OR. I see a lot of surgeons who make a quick mark and use that to guide the alignment. This is a much more accurate way to proceed. With intraoperative aberrometry, you can be very confident of your correction.”

Dr. Stephenson adds that the technology is most worthwhile if you take maximum advantage of it. “The holy grail is a great IOL power formula, but I find that ORA is excellent at picking the power of the implant,” she says. “I use it on 99 percent of my patients, and I change my power choice about 52 percent of the time based on what ORA tells me. I have state-of-the-art equipment for making preoperative measurements, and the ORA agrees with the predictions based on that data much of the time. If my information going into the OR is confirmed by ORA, that’s great. But if I have to
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hedge one way or the other, I always go with ORA.”

Dr. Hill says he plans to use intraoperative aberrometry with every cataract patient. “Less than 1 percent of surgeons are at ±0.50-D accuracy for 92 percent or more of their patients,” he says. “Only 6 percent achieve this accuracy for 84 percent of their patients. Everyone else is at about 78 percent. That’s the reality. Certainly, if you’re putting in a multifocal or toric lens, something you charge the patient extra for, surgeons in general need to up their game. HOLOS will be one way to do this.”

“If 90 percent of the surgeons using this technology get within 0.5 D of their target, why wouldn’t you want to be one of those surgeons?” asks Dr. Stephenson. “Today, the world is full of post-LASIK and post-refractive surgery patients. They want the same ‘wow factor’ that they got with LASIK. The only way to do that is with a technology like intraoperative aberrometry.”

**Just the Beginning**

“Intraoperative aberrometry technology is still in its early stages,” notes Dr. Liang. “Right now, we’re trying to figure out exactly how to use this technology. If you’re straddling between two powers that are close, the intraoperative aberrometry reading can push you towards one or the other. But if the aberrometer gives you a very different number than your preoperative calculations, then you have to use your brain. Are things lined up? Is the eye not staring at the fixation light? Is the surface too dry? Did I not have the correct pressure inside the eye? The real-time feedback helps the surgeon decide whether an unexpected reading is worth taking seriously, because changes in the readings are often associated with real-time actions such as pushing on the lid speculum.

“When topography first became available,” he adds, “some people said, ‘I don’t need topography to do cataract surgery or LASIK.’ But as we learned to use the systems and the technology improved, its importance became obvious. Today, no one would say that they can do cataract surgery without topography. I think intraoperative aberrometry will follow the same path. Someday, hopefully, this will be the standard of care.”

“Today, things like getting your patients’ residual astigmatism below 0.5 D are crucial if you want to have happy patients. To achieve that, you need technology like this.”

— Dee Stephenson, MD

Dr. Liang adds that no matter how good intraoperative aberrometry gets, it will never replace good preoperative measurements. “I would never tell someone that because you have an ORA or HOLOS you can turn off your brain and skip the detailed preoperative measurements,” he says. “What intraoperative aberrometry adds is another piece of information. If we want to do refractive cataract surgery we have to at least have a goal of coming close to LASIK outcomes. Intraoperative aberrometry will help us move in that direction.”

Dr. Linder says Clarity Medical Systems hopes to obtain the CE Mark for HOLOS later this year, in time to launch the upgraded version of the system that will incorporate the new IOL formula, at the European Society of Cataract and Refractive Surgery meeting. “After that,” he says, “we’ll continue to refine the algorithm as data comes in and continue to refine the physician portal so that the surgeon can get reports on his outcomes in comparison to baseline data and the overall database. We’ll be able to provide customized physician factors based on things like the surgeon’s style of wound and the location of the incision. We anticipate that this level of customization will help surgeons further improve their outcomes.”

Dr. Stephenson says she hopes the HOLOS system will eventually be just as good as she finds the ORA to be. “This is just the tip of the iceberg,” she says. “The great thing about technology is that it promotes competition from many companies and challenges the technology that’s already on the market to become even better. There are some brilliant engineers behind ORA, so I can’t wait to see what will come next.

“If I had to pick one instrument that I could use in the OR that would make my patients happier and improve their outcomes, it would be ORA,” she adds. “I wouldn’t choose a femtosecond cataract surgery system, because if your preoperative measurements are wrong, it doesn’t matter how precise your surgery is. Today, things like getting your patients’ residual astigmatism below 0.5 D are crucial if you want to have happy patients. To achieve that, you need technology like this.”

**Dr. Stephenson was previously a consultant for WaveTec. Drs. Liang and Hill are consultants for HOLOS.**

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Femtosecond Cataract: Dodge the Pitfalls

Walter Bethke, Managing Editor

Capsulotomy and lens fragmentation are key steps during which a case can falter.

Though femtosecond laser-assisted cataract surgery can help some surgeons improve their ability to create capsulorhexes and remove the nucleus, it’s not perfect and still carries the risk of various complications. Being forewarned is forearmed, however, and the expert surgeons in this article are more than willing to warn you about potential problems and how to avoid them. To learn how to improve your outcomes with FLACS, read on.

Achieving Good Dilation

Miosis is a potential problem with femtosecond-assisted cataract surgery that you can head off at the pass; it occurs in up to 32 percent of cases according to one study.1 Here is how experienced surgeons deal with it.

Though the miosis occurs after the femtosecond step, surgeons take preop steps to prevent it. “I published a small study a few years ago explaining how to prevent the 25-percent risk of pupillary miosis after the femto step,” says Singapore’s Ronald Yeoh, FRCS, FRCOphth, DO. “Miosis can be reduced significantly by the simple expedient of using an NSAID drop along with the dilating drops an hour or two before surgery.”

Robert Weinstock, MD, assistant professor of ophthalmology at the University of South Florida, Tampa, says timing also plays a role. “Give the patient extra time in the holding area,” he advises. “Don’t bring him back to surgery until you’ve given him adequate time to dilate. After that, we use a Shugarcaine type of mixture containing lidocaine and epinephrine on small pupils right after we make the cataract wounds but before we put the viscoelastic. We also use a drop of 10% phenylephrine in all patients immediately after the femto laser step, unless they have a cardiac disorder or hypersensitivity to the drug. We also may use the phenylephrine in preop for a patient who’s not dilating, but that’s not routine. In addition, we will use Omidria as long as it’s on a plan or the insurance covers it.

“There’s something else to note about small pupils,” Dr. Weinstock continues. “The closer the capsulotomy is to the edge of the pupil, the more collateral laser energy will hit the pupillary rim, which can induce some miosis. The patients whose pupils shrink down a little and get some miosis right after the laser treatment are the ones who start out with smaller pupils, because you’re getting the laser energy so close to the pupillary margin.”

Even if the patient’s pupil is relative-
ly small, some surgeons are able to create a usable capsulorhexis. “If he hasn’t dilated completely, you have to make a decision—and sometimes you can’t make that decision until he gets to the laser—about how big of a capsulotomy you can squeeze inside the pupil,” explains Dr. Weinstock. “Every doctor has a different comfort level; some will shrink capsulotomies down to sub-5 mm, and some will shrink them down to sub-4 mm. In general, though, if you’re uncomfortable that the pupil is too small once you dock the patient, you can bypass the laser capsulotomy and fragmentation and just do the astigmatic correction with the laser. If you feel the pupil is big enough to do the case successfully, you can shrink your standard capsulotomy, say, from 5.5 mm to 5 or 4.8 mm, and just squeeze it inside the pupillary margin.”

**Applanation and Docking**

Occurring in about 2 percent of cases, a suction break is one of the recognized complications of femto-assisted cataract surgery that can momentarily, or permanently, derail the femto portion of the procedure.1 Here are surgeons’ thoughts on achieving good applanation and maintaining suction.

London surgeon Sheraz Daya says the quality of the applanation can directly affect the quality of your femtosecond treatment. You need to applanate without producing wrinkles on the posterior aspect of the cornea, because wrinkles will cause the laser energy to be focused in the wrong place,” he says. “In fact, you won’t get any effect at all because the cavitation bubbles won’t form due to the laser being out of focus. That’s how you get tags and skips in the capsulotomy. We use the so-called soft-docking method in which we put fluid in the suction ring and applanate just enough to make contact with the eye in the center but leave a meniscus of fluid in the periphery. That way, we can see whether we’re producing wrinkles in the posterior cornea or not.”

Dr. Weinstock says patient awareness can help avoid suction breaks. “You have to make sure the patient is lightly sedated,” he says. “If she’s overly sedated, she will fall asleep, and then suddenly wake up with a jerk. It’s when you have this kind of patient movement that suction breaks and complications can occur. It’s a situation very much like LASIK, in which you can use your voice as a ‘vocal local’ anesthetic; with a calming voice, tell the patient what you’re doing at each step to keep her calm.

“If you do get a suction break, unless you haven’t done any femtosecond treatment at all, my advice is to abandon the surgery,” Dr. Weinstock continues. “Practically speaking, you can usually finish the rest manually. Also, if any complication occurs with the femtosecond surgery—whether it’s an incomplete treatment or a suction break or something else—make a note of it, because afterward the patient may go back into holding or you may have done some other tasks before seeing her again for the cataract portion, and you’ll need a reminder that something unusual occurred.”

**Capsulotomies**

In the study cited earlier regarding miosis issues, the surgeons also experienced a 20-percent incidence of issues with the femtosecond capsulotomy, including capsule tags and bridges, and a 4-percent incidence of anterior tears.1 Surgeons say, however, that you can dramatically reduce your risk of these problems by making certain adjustments to the laser, as well as to your technique.

Springfield, Mo., surgeons Shachar Tauber, Wendell Scott and their colleagues have won the American Society of Cataract and Refractive Surgery’s best paper of session award two years running for their work on adjusting the femtosecond laser’s settings to create better capsulorhexes. “First, if at all possible, use a programmable setting that lets you center the capsulotomy on the geometric center of the capsule,” Dr. Tauber says. “If there’s a lot of tilt in the lens—such as when the patient has a Bell’s phenomenon—either reacquire the image to get a more anatomically correct one or turn off capsule centration and use pupil centration so you’re not using the laser on a tilted lens or eye. Using it on a tilted lens can result in partial cuts into the capsule in one location and deeper cuts on the opposite side. Also, along with pupil centration, you can customize the diameter. We use a 4.9-mm diameter usually, but can go up to 5.1 or 5.2 mm or so. There may...
be a benefit to doing a large capsulotomy, such as 5.5 mm, in patients with pseudoexfoliation because there may be less chance of phimosis and less stress on the zonules later on. A larger, more consistent capsulotomy also may help in cases of late IOL decentrations/dislocations.

“One of the most pressing issues we found when reading the femtosecond cataract literature is the increased risk of capsular tears,” Dr. Tauber continues. “Scanning electron microscopy studies were showing how aberrant laser pulses create almost a postage-stamp capsulotomy and/or extra pulses on the uncut part of the capsule. In response, my colleague Dr. Wendell looked at the parameters we could change on the femto capsulotomy, and one was the vertical spacing between the rings of photodisruption the laser creates as it makes the capsulotomy. The laser comes with a 10 µm vertical spacing, so in 2015 we changed it to 15 µm and immediately noticed a statistically significant decrease in the amount of ‘slivers,’ or little pieces of capsule that flop around at the end of the case, as well as a decrease in our already low anterior capsule tear rate. This year, we did another 1,000 cases in which we increased the vertical spacing to 20 µm. The sliver rate didn’t change significantly, but the anterior capsular tear rate decreased to 1.1,000, which was a significant improvement.

“The other change we implemented was timing the capsulotomy so that it’s synchronized with the patient’s exhalation,” Dr. Tauber adds. “This is because an exhale is very steady and involves limited head movement, while an inhale involves more head movement that can result in aberrant laser pulses during the capsulotomy creation. Also, in studies we reviewed in which the tear rate was high, we felt it was due to the amount of time required for the capsulotomy, so we reduced the two-second capsulotomy to 0.8 seconds. I think the combination of increased vertical spacing and the timing and quickness of the capsulotomy allowed us to decrease our tear rate.”

Nashville, Tenn., surgeon Ming Wang says that surgeons need to be aware that, since the femtosecond separates tissue by creating a series of microscopic bubbles joined by uncut tissue, the tissue might not be cut in all areas of the capsulorhexis. “You have to be careful when detaching the circular capsulorhexis cap from its peripheral rim,” he says. “If you’re not careful, you can produce radial tears if you don’t press it down in the center first.”

**Incision Issues**

Surgeons say one of the laser’s basic functions that gives the most headaches is the creation of the cataract entry wound and paracenteses.

“Creating the entry wound and a paracentesis is a well-recognized limitation of all femtolaser platforms,” says Dr. Yeoh. “What you see is not what you get. In other words, an incision placed at a certain location on the system’s screen actually appears in a slightly different location on the cornea itself. Certain laser platforms that use a variable aperture are better at delivering pulses to the corneal periphery so that incisions are usually patent and well-located, though. The surgeon should get used to his individual femtolaser machine in order to understand where the incisions end up, and factor this in when he chooses the incision location.”

Many surgeons just pull out the diamond blade when it’s time to make the entry wounds. “I’ve been very unimpressed with the laser’s ability to cut through peripheral opaque tissue [when making the initial incision],” avers Dr. Weinstock. “Most patients have some opacity or areas to their limbus, right where you want to put the wound. And it’s kind of hit or miss as to whether someone has that, since you can’t really tell during the docking step because the visualization usually isn’t good enough to see that area in detail. So, quite a bit of the time, after trying the laser, I end up having to use the diamond blade anyway to complete the incision, which results in an irregular wound because I’m trying to find the track of the laser incision. Then, when I put the blade through that track I wind up getting false tracks and extra wounds. So, instead of the laser, I just use a diamond blade first so the wounds are in the exact same spot each time.”

**Femto-fragmentation**

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The most common adverse reaction observed in controlled clinical studies with TRAVATAN Z\textsuperscript{\textregistered} Solution was ocular hyperemia, which was reported in 30 to 50\% of patients. Up to 3\% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10\% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus. In postmarketing use with prostaglandin analogs, periocular and lid changes including deepening of the eyelid sulcus have been observed.

Use in Specific Populations
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

For additional information about TRAVATAN Z\textsuperscript{\textregistered} Solution, please see the brief summary of Prescribing Information on the adjacent page.

References:

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USE IN SPECIFIC POPULATION

Pregnancy
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Questions regarding teratogenic effects of travoprost in rats at an intravenous (IV) dose up to 10 mg/kg/day (250 times the maximal recommended human ocular dose (MRHD)), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, demed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 mg/kg/day (75 times the MRHD), or in mice at subcutaneous doses up to 1 mg/kg/day (25 times the MRHD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 mg/kg/day (75 times the MRHD) and in mice at subcutaneous doses > 0.3 mg/kg/day (7.5 times the MRHD).

In offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of ≤ 0.12 mg/kg/day (2 times the MRHD), the incidence of postnatal mortality was increased, and the recommended body weight gain was also affected, evidenced by delayed eye opening, prenaal detachment and prenaal separation, and by decreased motor activity.

There are no adequate and well-controlled studies of TRAVATAN® (travoprost ophthalmic solution) 0.004% per ophthalmic solution in pregnant women. Because animal reproductive studies are not always predictive of human response, TRAVATAN® Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN® Solution is administered to a nursing woman.

Pediatric Use
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

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

Hepatic and Renal Impairment
Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHD) of 0.04 mg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay.

A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S9 activation obtained at 40 mcg/ml, concentrated to 10 mg/ml. Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mg/kg/day by 250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mg/kg basis (MRHD) at 10 mg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mg/kg/day (75 times the MRHD).

PATENTS
U.S. Patent Nos. 5,631,287, 5,899,052, 6,011,062, 6,235,781, 6,503,497, and 6,849,253

Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Rx Only
U.S. Patent Nos. 5,631,287, 5,899,052, 6,011,062, 6,235,781, 6,503,497, and 6,849,253
to do it, however, that are safer or more effective than others, surgeons say.

London’s Dr. Daya says the laser configuration the surgeon chooses can help protect the ocular anatomy during phaco. “For hard lenses, I usually make two small rings in the center of the nucleus to get rid of the sharp edges,” he says. “If the pieces are sharp, if any of them were to go in a direction that I didn’t want—such as forward—it could cut the capsule. Soft lenses, on the other hand, are tricky because you can’t rotate them. They’re easy to take away once you’ve got a hold of them, but they stick to the capsular bag more.”

Dr. Wang says it pays to know how the laser interacts with tissue when fragmenting the nucleus. “How deep the laser can travel into the nucleus and remain effective depends on the density of the lens,” he explains. “The denser the lens, and the deeper the travel, the less efficient the femtosecond laser’s cavitation bubble will be in separating the tissue; shots are reduced in laser intensity when they reach the tissue that’s more posterior in a denser lens. This means your potential cut is even weaker on the backside of the lens. Understanding this is important to avoid having a false sense of security that all those cuts are truly separating the lens. Those rings and crosses may not actually be cut. So, with a denser cataract, after you’ve done the femto-fragmentation, you almost have to ignore that the lens has been pre-chopped. You’ll be safer this way because you’ll pay more attention to your manual maneuvers. If you’re too cavalier about it and just go in and assume those lines actually show tissue separation, you can break the capsule. Remember, the lines the laser creates are just lines of potential separation.”

**Modified Hydrodissection**

Due to either intracapsular gas created during femtosecond nuclear fragmentation or fusion between the cortex and anterior capsule—or a combination of both—surgeons avoid traditional hydrodissection when doing FLACS, since it can result in tears. The translenticular approach, developed by Dr. Daya, is a good alternative.

Dr. Daya’s approach is performed after femto-fragmentation. “I use a device I designed with B + L that looks like a phaco chopper but is actually a cannula,” he explains. “Using the instrument, I go through one of the fragmentation lines into the mid-periphery of the lens—where it’s softer—and gently inject fluid,” he explains. “I then look for a fluid wave and displacement of the posterior gas bubble. While I’m irrigating, I’ll turn the lens. When it rotates, then I know I’ve hydrodissected properly.” (See image, above)

Dr. Daya says this technique can be especially helpful with soft lenses. “Soft lenses are tricky because you can’t rotate them,” he says. “I’ve found that if I do a translenticular hydrodissection, I’ve got to get a nice push

**Other Pearls**

Surgeons offer other bits of advice to improve the femtosecond laser’s performance in general and in unique situations.

- **Power setting adjustments.** Dr. Tauber says that doubling the laser’s energy output, usually from 4 to 8 µJ, in patients with a scar from herpes or trauma, as well as in patients with a history of corneal surgery, allows for better penetration of the beam. “Also, increase the cut depth from 500 to 800 µm in a cornea with disease such as Fuchs,” he says, “because the corneal disease can potentially limit the energy penetration.”

  “Another instance in which we’ll change the energy settings and depth is in patients in whom we place a capsular tension ring,” Dr. Tauber adds. “This is because these devices are implanted under viscoelastic and, no matter how much viscoelastic we remove afterward, there’s always some left in the eye that can interfere with the laser. Increasing the energy in these patients makes the risk of an(continued on page 59)
At Last, Cross-Linking Comes to U.S. Surgeons

Michelle Stephenson, Contributing Editor

The FDA approved long-awaited corneal collagen cross-linking for the treatment of keratoconus.

In April, the Food and Drug Administration approved Avedro’s Photrex, Photrex and the KXL System for the treatment of progressive keratoconus. Here is a rundown of how the system works from surgeons familiar with it.

New Approach

Photrex Viscous and Photrex are photoenhancers indicated for use in corneal collagen cross-linking with the KXL System.

“This is a brand-new approach and a brand new surgical platform that really represents an advance in the treatment of keratoconus,” says Peter Hersh, MD, medical monitor for the FDA trial and in private practice in Teaneck, N.J.

Michael Raizman, MD, who is in private practice and on the faculty at Tufts Medical School in Boston, agrees. “This is important for keratoconus patients in the United States,” he says. “We have been waiting for this approval for years. Patients in this country have been able to get these treatments through clinical trials, and some doctors have acquired devices and are performing treatments without FDA approval; however, most doctors and patients may feel most comfortable when they are using an FDA-approved drug and device. Because there is no other treatment to prevent the progression of keratoconus, cross-linking has already revolutionized the treatment of keratoconus around the world. It has been available in Europe for more than 15 years and for many years in most other countries. The United States has just been very slow to reach this point.”

Treating Keratoconus

Keratoconus is the most common corneal dystrophy in the United States, affecting approximately 170,000 Americans. It causes the cornea to bulge, creating an abnormal curvature that changes the cornea’s optics, producing blurred and distorted vision that is difficult to correct with glasses. This progressive thinning and weakening can result in significant visual loss and may lead to the need for a corneal transplant.

“With the approval of cross-linking, most patients will no longer require corneal transplantation,” Dr. Raizman says. “Cross-linking prevents the progression of the disease in nearly all patients who undergo the treatment. One treatment is enough for nearly every patient. It is a very safe, comfortable treatment, so the postoperative recovery is quite manageable with
minimal discomfort for all patients including children.”

As a one-time treatment, it is much less expensive than a corneal transplant, which may need to be repeated. “Many of these patients are quite young when they have their first transplant, so they will need multiple transplants, multiple doctor visits after each transplant, and usually eye drops forever,” Dr. Raizman says. “If you add up the total cost, it is probably on the order of forty- or fiftyfold less expensive to treat with cross-linking,” Dr. Raizman adds.

The FDA approval was based on Avedro’s NDA submission, which included data from two prospective, randomized, parallel-group, open-label, placebo-controlled, 12-month trials conducted in the United States to determine the safety and effectiveness of Photorexa Viscous and Photorexa when used for performing corneal cross-linking in eyes with progressive keratoconus. Study 1 included 58 patients with progressive keratoconus, and Study 2 included 147 patients with progressive keratoconus. In each study, one eye of each patient was designated as the study eye and was randomized to receive either cross-linking or sham.

The cross-linked eyes demonstrated increasing improvement from month three through month 12 in Kmax, which is defined as the maximum corneal curvature. Progressive keratoconus patients had an average Kmax reduction of 1.4 D in Study 1 and 1.7 D in Study 2 at month 12 in the cross-linked eyes and an average Kmax increase of 0.5 D in study 1 and 0.6 D in study 2 at month 12 in untreated eyes. The difference between the cross-linked and untreated groups in the mean change from baseline Kmax was -1.9 (-3.4, -0.3) D in Study 1 and -2.3 (-3.5, -1.0) D in Study 2.

In clinical studies, the most common ocular adverse reactions observed in treated eyes were corneal opacity (haze); punctate keratitis; corneal striae; corneal epithelial defect; eye pain; reduced visual acuity; and blurred vision.

“The FDA approval of Avedro is a gigantic leap forward for ophthalmologists in the United States,” says A. John Kanellopoulos, MD, who is in private practice in Athens, Greece and in New York City. “It is well-known through the global experience that corneal cross-linking has become the standard of care for stabilizing keratoconus and corneal ectasia. I am personally very excited that this treatment will be available to everyone who is in need in the United States, and I am also excited about the body of clinical work and clinical research that relates to this treatment that is being produced by U.S. clinicians and has been missing all these years in the ophthalmic literature and at ophthalmic meetings.”

How It Works

According the Dr. Kanellopoulos, cross-linking entails removing the corneal epithelium, using either an epithelial brush, diluted alcohol or manual scraping. “Some clinicians tend to prefer an excimer laser scrape of the epithelium,” he says. “In my opinion, this would also add a significant topography-guided normalization in these irregular corneas because the epithelium tends to be irregular. So, a standard PTK of 50 µm would shave off part of the central cone and improve the cornea normality to a degree to have the patient gain anywhere from one to five lines of vision.”

After the epithelium is removed, the cornea is soak with riboflavin drops placed over a 30-minute period. “Then, the KXL device is placed over the patient’s eye, which is usually held open with a lid speculum,” he says. “We anesthetize with topical anesthetic, usually one drop of proparacaine or Alcaine replenished every 10 to 15 minutes, depending on the patient’s tolerance. The device has a timer with an LCD screen to help the clinician evaluate the progress of the procedure. The surgeon and the staff reinforce patient compliance by letting the patient know how many minutes are left in the treatment. Following the procedure, some clinicians patch the eye, and some use a bandage contact lens. Antibiotic medications and corticosteroids are typically used for one to four weeks, and eyes are typically protected from UV light for two months.”
Although corneal cross-linking has been found to be a safe procedure, complications such as infectious keratitis can occur. “If the device is placed too close to the cornea, there may be a higher amount of energy delivered, which can scar the cornea,” Dr. Kanellopoulos says. “Also, an immune ring has been described after the procedure that may relate to the bandage contact lens use or an immune reaction of the cornea to the procedure; it usually resolves with topical corticosteroids. Cornea melt resembling central toxic keratopathy has been described as well, although all of these are extremely rare complications.”

According to Dr. Hersh, “Cross-linking is much like putting extra wires on a suspension bridge to make the bridge stronger,” and it is very effective. He and a colleague recently reviewed the outcomes of corneal collagen cross-linking for keratoconus or ectasia in a cornea subspecialty practice. The study included 104 eyes (66 had keratoconus and 38 had ectasia). The investigators reviewed the outcomes and the natural course of changes in postoperative parameters including Kmax, uncorrected visual acuity and best-corrected visual acuity over 12 months.

At one year, an average of 1.7 D of flattening in Kmax was observed. Mean best-corrected visual acuity improved slightly more than one line (from 0.35 ±0.24 to 0.23 ±0.21 log-MAR). All postoperative parameters worsened between baseline and one month and improved thereafter. The study found that eyes with a preoperative Kmax of 55 D or steeper were 5.4 times more likely to gain 2 D or more of Kmax flattening at one year after cross-linking. Additionally, eyes with a preoperative best-corrected visual acuity of 20/40 or worse were 5.9 times more likely to gain two or more Snellen lines at one year after cross-linking.

This study demonstrates that corneal collagen cross-linking can effectively decrease the progression of keratoconus, with improvements in optical measures in many patients. “Generally, the trend observed was immediate worsening between baseline and one month, resolution at approximately three months and improvement thereafter,” the authors wrote. “In predicting outcomes after cross-linking, no patient characteristics showed correlations with negative treatment outcomes such as loss of vision or continual topographic steepening. However, steeper Kmax (≥55 D) and poorer best-corrected visual acuity (≤20/40) at the time of treatment correlated with better postoperative Kmax and best-corrected visual acuity outcomes at one year, respectively. These outcome predictors should be considered when offering cross-linking to patients with keratoconus or postoperative corneal ectasia.”

As mentioned earlier, a one-time treatment for stabilizing keratoconus is especially beneficial in children, and cross-linking has also been found to be effective in this patient population. A recent study conducted in Switzerland included 33 eyes in 25 patients who were 18 years or younger. Follow-up visits occurred after each of the first four years. Progression was defined as an increase in Kmax of at least 1 D in one year. Prior to the cross-linking procedure, patients’ mean Kmax was 55.3 ±7.3 D, which decreased significantly after one year to 53.4 ±7.4 D. Progression was stopped in 23 patients, and five cases of presumed progression were identified. One case had significant steepening in Kmax four years after cross-linking, but the topographic parameters were unchanged. Repeat topography showed that the Kmax was stable. Two cases with limbal vernal keratoconjunctivitis worsened in both corneal tomography and topography.

After resolution of the limbal inflammation, the Kmax values returned to their pre-inflammation values. Additionally, there were two cases of true progression, both of which had advanced keratoconus prior to cross-linking (preoperative Kmax of 64.4 and 75.1 D, respectively).

The Future

According to Rajesh Rajpal, MD, who is in private practice in the Washington, DC, area and is also chief medical officer for Avedro, cross-linking is currently being studied outside the United States as a refractive procedure (photorefractive intrastromal corneal cross-linking [PiXL]). “This uses the Mosaic System by Avedro and different formulations of riboflavin, he says. “It is a customizable cross-linking treatment for low levels of myopia that is being studied transepithelially as well as with removing the epithelium.”

Patients who are good candidates for this procedure are in the relatively low myopia range (0.75 to 2 D). These are patients who don’t typically opt for a refractive procedure because they consider LASIK and PRK as too invasive. “This procedure has had good results transepithelially,” Dr. Rajpal says. “Depending on how trials outside the United States continue to go, and so far they have been very positive, the company would then plan to work with the FDA to have the Mosaic device and those formulations of riboflavin start clinical trials in the United States. Mosaic already has a CE mark in Europe.”

All four doctors interviewed for this article have a financial interest in Avedro.

1. Data provided by Avedro Inc.
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I am a pediatric cataract surgeon who also does, comprehensively, many other ophthalmic surgeries on children including procedures for strabismus, eyelid ptosis, orbital lesions, nasolacrimal duct blockage and a variety of anterior segment and corneal diseases. However, the only adults I operate on are those with strabismus. It may seem unusual for a surgeon to do cataract surgery only on children. However, in the United States, many pediatric surgeons do so. This fact speaks to how different the medical decision-making and the surgery itself are from the standard adult procedure. The fact that I don’t operate on adults with cataracts does not mean that I do not keep up with the constant flow of innovations being developed in the higher volume and more lucrative adult cataract market. I listen carefully, and I watch intently. With the knowledge and experience I have in the pediatric sphere, I carefully pick and choose techniques that are applicable to the eyes of children. In some cases, techniques are borrowed from both the adult cataract and the adult retina subspecialty areas (See Figure 1).

In pediatrics, our first decision is when to operate, if surgery is even indicated at all. Adult cataract surgery is thought of as a refractive procedure that can correct hyperopia, myopia and astigmatism in a precise and predictable manner. Pediatric cataract surgery removes the all-important offset to changes in globe axial length,—the growing and pliable young lens—irreversibly derailing the eye’s natural emmetropization.

Deciding when or whether to operate on a partial cataract in a pre-literate toddler with anisometropia and amblyopia can be daunting. Even if glasses and patching are started first, compliance may be an issue and quantitating improvement from these non-surgical first steps may be nearly impossible. A rush to surgery may be appropriate, but it renders the eye permanently presbyopic and subject to a large and somewhat variable myopic shift over time. Children may be more spectacle-dependent after surgery than before surgery. On the other hand, excessive delays in surgery may worsen form-vision deprivation, and this may drastically change the eye-growth feedback loop, resulting in excessive axial elongation. Admittedly, it is an art. Experience in pediatric assessment is as critical as the acquisition of surgical skills (See Figure 2).

The fact that general anesthesia is operating on these young patients can be uniquely challenging but highly rewarding.
usually required also makes pediatric cataract surgery less efficient and more time-consuming. Biometry often has to be done after the child is asleep. Microphthalmia, pre-existing capsular abnormalities and even congenital retinal abnormalities may be found at the surgical exam-under-anesthesia.

Surgeons who underestimate the differences between surgery on a young child and surgery on the elderly may find themselves struggling in the operating room. The lack of a hard nucleus, vastly reduced scleral and corneal rigidity and enhanced posterior vitreous pressure demand a surgical approach that differs in many ways from the adult procedure. After surgery, the surgeon must deal with an increased propensity for postoperative inflammation and capsular opacification; a refractive state that is constantly changing due to growth of the eye; difficulty in documenting anatomic and refractive changes due to poor cooperation and compliance; and a tendency to develop amblyopia.

Pediatric Cataract Pearls

For the procedure itself, here are a few pearls that I have learned over the course of nearly 30 years of operating on children with cataracts.

1. **Stitching the wounds is the safest approach.** I attribute the poor self-sealing to low corneal rigidity resulting in fish-mouthing of the wound, leading to poor approximation of the internal corneal valve to the overlying stroma. The recommended closure material is a 10-0 synthetic absorbable suture.

2. **Bimanual irrigation and aspiration works best.** Pediatric cataracts are soft, but they may be “gummy.” Working one instrument against the other can squeeze the cortex into the aspiration port. A curved irrigation cannula can also be used to gently and continuously hydrodissect lens material out from the equator of the bag.

3. **When tearing the highly elastic capsules of children, the capsulorhexis force vector must often be directed more toward the center of the pupil in order to control the turning of the CCC edge along a circular path.** I re-grasp the capsulorhexis edge frequently and begin with a smaller capsulotomy than desired. Because of the elasticity, the opening will be larger than it appears once the forceps release the capsule flap.

4. **Don’t fear the vitrectomy.** It is vitreoretinal traction that should be meticulously avoided. A primary posterior capsulotomy and an anterior vitrectomy during intraocular lens implantation in the young child gives the best chance for maintaining a long-term clear visual axis (See Figure 3).

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incidences of cystoid macular edema and retinal detachment are exceedingly rare after capsulectomy and vitrectomy in children. Anterior segment surgeons are often more accustomed to, and more comfortable with, a limbal (or anterior) approach to the vitreous. However, I prefer to perform these procedures via the pars plana/plicata, with the irrigation cannula remaining in the anterior paracentesis (See Figure 4).

5. Intracameral medications are key and can militate against post-operative non-compliance, which is more common in children than adults. After the surgical wounds have been closed, I place intracameral antibiotics in the eye. Currently I am using 0.1 cc of a 50% solution of moxifloxacin (Vigamox, Alcon). Alternatively, 0.05 cc of undiluted Vigamox can be used. There is no preservative in Vigamox, and its safety in the anterior
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chamber has been studied. I also inject 1 to 2 mg (0.025 to 0.05 cc) of triamcinolone (Triesence, Alcon) into the anterior chamber at the end of surgery in most children. The triamcinolone crystals are visible in the anterior chamber for five to seven days and help control the aggressive early inflammation that can be present in children.

6. For children under 7 months of age, it may be best to leave the eye aphakic and prepare the parents for a secondary IOL in the preschool or early grade school ages. This approach, when applicable, is less traumatic for the infant eye, and reoperation is less common than when an IOL is inserted early in life. When I use this approach, I place a Silsoft (Bausch & Lomb) extended-wear silicone contact lens on the eye at the end of surgery without a patch or shield. Since I don’t place any subconjunctival injections, the eye is white and quiet and the image well-focused from the outset. A lens constant of 112.176 is used with biometry to select the Silsoft contact lens power. The initial lens can stay in place for the entire first postoperative month. After a four-week course of postoperative drops has been completed, the parents are taught to remove and clean the contact lens weekly.

7. When placing an IOL in a child’s eye, in-the-bag implantation is strongly recommended, although we have observed that some IOL designs are very well-tolerated in the child’s ciliary sulcus even after many years of follow-up. When using your IOL of choice, it is important to customize the A-constant after analysis of your pediatric results separately from your adult cases.

Surgical management of cataracts in children is markedly different from adults. The eyes are not only smaller because of age but many are also microphthamalic. Decreased scleral and corneal rigidity and increased posterior vitreous pressure make surgical manipulations within these eyes more difficult. The anterior chamber is often unstable; the capsule management requires special considerations. Variability in ocular growth makes selection of an intraocular lens power less certain. Normal childhood behavior may reduce compliance with postoperative instructions, even when the parents are diligent. Finally, examinations of the eye after surgery may be less detailed and precise when cooperation is lacking. The long expected lifespan after surgery for children also deserves consideration when surgical decisions are made. These special patients are uniquely challenging but caring for them as they mature and grow from children into adults is immensely gratifying.

Dr. Wilson is a professor of ophthalmology and pediatrics at the Albert Florens Storm Eye Institute at the Medical University of South Carolina in Charleston. He holds the N. Edgar Miles Endowed Chair in Ophthalmology. He is the current president of the American Association for Pediatric Ophthalmology & Strabismus (AAPOS) and the council chair for the American Ophthalmological Society. He is a Senior Honor Award recipient from the American Academy of Ophthalmology and a Lifetime Achievement Award recipient from AAPOS. The second edition of his textbook with Rupal Trivedi entitled: Pediatric Cataract Surgery: Techniques, Complications and Management, was published in 2014. Contact him at wilsonme@musc.edu.
A sure sign that summer is on its way is the annual congress of the Association for Research in Vision and Ophthalmology. ARVO returned to the great Northwest this year, with another week of spectacular weather and superb science. As in years past, we surveyed some of the many presentations, and now provide this sampling of a few of the posters and presentations that caught our eye.

(Unless otherwise specified, all of the abstract citations are from this year: IOVS 2016; 57.)

**Gene Therapy**

Identification of specific disease-associated genes using next-generation sequencing has made personalized medicine a reality for patients who suffer from congenital disorders. This year at ARVO, presentations focusing on personalized medicine were dominated by application of CRISPR/Cas9 technology. CRISPR, an acronym for “clustered regularly interspaced short palindromic repeats,” is a mechanism that allows for directed, specific splicing of a disease-associated gene, thereby removing the genetic identity of a particular condition. While the methodology holds great promise, technical hurdles remain, such as splicing the wrong gene, a problem that can be significant in some applications. Despite this, the promise of CRISPR was clearly seen in the explosion of presentations at this year’s ARVO.

One group investigated the use of CRISPR-based genomic editing for the treatment of CEP290-associated Leber congenital amaurosis. This study demonstrated that CRISPR-based genome editing deleted the most common human mutation in CEP290, suggesting a clinically meaningful way to restore CEP290 function without the risk of overexpression toxicity. (Stone E, et al. ARVO E-Abstract 1838) The use of CRISPR in the treatment of retinal degenerative diseases, such as retinitis pigmentosa, was also investigated. Researchers at the University of California, San Diego, developed genetically modified, human, induced pluripotent stem cell (hiPSC) retinal cell-reporters using CRISPR technology. Using this approach, the authors identified novel mechanisms of retinal development that potentially could increase the efficiency and pace of photoreceptor generation. (Wahlin K, et al. ARVO E-Abstract 2820) Look for an upcoming Therapeutic Topics to provide an in-depth look at CRISPR/Cas9 technology and its future in ophthalmology.

Many presentations focused on more traditional gene therapy using nonpathogenic viruses as delivery/vector systems (e.g., adeno-associated viruses or lentiviruses). Although this technique is technically challenging, a decade of research and development has yielded significant progress. A clinical study of RetinoStat (Oxford BioMedica), a lentiviral vector expressing endostatin and angiostatin, was one of this year’s many applications of viral-based gene therapy. (Lauer A, et al. ARVO E-Abstract 4719) The study was conducted by consultants and researchers from Oxford BioMedica. RetinoStat was administered subretinally to 21 patients with poor anti-VEGF response as a possible treatment for advanced neovascular AMD. The vector safely delivered the two transgenes and led to visual acuity stabilization and reduction of vascular leakage. In an-
other presentation, intravitreal delivery of AAV-mediated expression of Stannicocalcin-1 (STC-1, Applied Genetics Technologies) delayed photoreceptor degeneration in two rodent models of retinitis pigmentosa; the researchers identified genes to investigate in future studies, mechanisms of action and the therapeutic potential of the approach. (One of the study’s researchers holds a patent on the therapy and consults for AGT.) (Roddy G, et al. ARVO E-Abstract 2737)

Stem Cell Biology

Stem cell technologies and applications were once again a popular topic at ARVO, with more than 150 posters and presentations covering developmental biology, cell fate regulation, novel stem cell markers and populations, and therapeutic applications. The focus of therapy included the corneal epithelium, stroma and endothelial layers; directed differentiation and transplantation of retinal cells; and even use of progenitor cells to understand congenital disorders.

A particularly popular topic was the therapeutic application of pluripotent stem cell-derived retinal pigment epithelium. One study showed that autologous, induced pluripotent stem cells can be successfully transplanted subretinally, and that the graft was well-tolerated a year after transplant. (Kurimoto Y, et al. ARVO E-Abstract 3769) Two studies took the allogeneic route and used RPE derived from human embryonic stem cells for the treatment of wet age-related macular degeneration (Yin Z, et al. ARVO E-Abstract 3742) or Stargardt’s disease. (Mehta M, et al. ARVO E-Abstract 3768) Both studies showed that the stem cell-based therapies were well-tolerated, leading the way to efficacy trials and, perhaps, successful treatments of these blinding diseases with stem cells.

Another hot topic in the stem cell field was the effect of stem cell secretory products and vesicles on cell differentiation and tissue repair. One study found that microvesicles secreted by hESC can induce de-differentiation and trans-differentiation in Müller cells. (Farber D, et al. ARVO E-Abstract 2921) Another group found that vesicles derived from human mesenchymal stem cells increased corneal epithelial cell proliferation, thereby promoting corneal wound repair and reducing corneal neovascularization. (Ritter T, et al. ARVO E-Abstract 3477) In a similar study, mesenchymal stem cells derived from bone marrow were shown to secrete factors that accelerate corneal epithelial wound healing, supporting the results of the previous study. (Eslani M, et al. ARVO E-Abstract 3478)

Dry-eye disease was another therapeutic target for stem cell treatment this year. There were two notable studies that used stem cells to either increase tear production or to regenerate tear-producing tissue. One study showed that intraperitoneal injections of bone marrow-derived mesenchymal stem cells increased tear production in a mouse model of Sjögren’s syndrome. (Aluri H, et al. ARVO E-Abstract 4921) This suggests that mesenchymal stem cells may act at a distance to treat dry-eye syndrome. Another study combined mesenchymal stem cells with lacrimal gland epithelial cells and human endothelial cells to create a functional lacrimal gland. (Massie I, et al. ARVO E-Abstract 5223) The group showed that, in defined culture conditions, the cells organized to form secretory spheroids that may eventually be used to replace damaged lacrimal gland tissue, restoring tear production in patients with dry-eye syndrome.

Retina

It was not too many ARVOs ago that anti-VEGF technology was at the cusp of clinical approval, similar to today’s viral gene therapy. Now, anti-VEGF therapy is an established therapeutic approach with indications that continue to be expanded and refined. Two presentations focused on switching treatment from ranibizumab to aflibercept. In one study, 26 patients with polypoidal choroidal vasculopathy who were previously refractory to ranibizumab received intravitreal injections of aflibercept. Visual acuity improved or was maintained for two years; however, subretinal fluid was still visible in approximately 30 percent of patients. (Kohno T, et al. ARVO E-Abstract 514) In a second Phase III multicenter trial of switching treatments, 82 wet AMD patients with RPE detachment who
One of the primary targets for gene therapy is retinitis pigmentosa, a group of inherited diseases featuring hyperpigmentation of the retina and progressive loss of visual function. hadn’t responded to ranibizumab were switched to intravitreal injection of aflibercept. This treatment change appeared to be effective in reducing PED volume and height and in improving visual acuity. (Gallemore R, et al. ARVO E-Abstract 4986)

A different treatment target for aflibercept, in addition to VEGF-A, was identified in galectin-1, an angiogenic factor associated with proliferative diabetic retinopathy. In *in vitro* and *in vivo* studies, including eye tissue from PDR patients, aflibercept bound to and neutralized galectin-1. This activity was independent of VEGF binding, suggesting that aflibercept may also be effective as an anti-angiogenic treatment for PDR. (Kanda A, et al. ARVO E-Abstract 1352)

New alternatives to aflibercept and ranibizumab are on the horizon, and research continues on brolucizumab for neovascular AMD. A Phase III, international, two-year efficacy and safety study of approximately 1,600 patients, sponsored by Alcon, is ongoing. Alcon hopes that brolucizumab, which is smaller than other anti-VEGF molecules, may have a longer duration of effect than current anti-VEGF drugs, allowing for fewer injections, thereby reducing the treatment burden for patients. (Dugel P, et al. ARVO E-Abstract 5018)

While the potential of anti-VEGF treatments is impressive, some patients have a suboptimal response to anti-VEGF therapies or don’t respond to them at all. As a result, researchers are looking into other treatments targeting different pathways that may provide important complements to existing anti-VEGF approaches. Several presentations at this year’s ARVO focused on combination therapies. Some of these targeted wet AMD refractory to anti-VEGF treatment, and others were designed to improve the efficacy of anti-VEGF therapies. In a study of 10 patients with neovascular AMD, addition of topical dorzolamide-timolol therapy to anti-VEGF treatment significantly reduced macular edema and subretinal fluid. (Sridhar J, et al. ARVO E-Abstract 4441)

In another study of 24 wet AMD patients with suboptimal responses to prior anti-VEGF therapy, a combination of anti-angiopoietin (Ang2) monoclonal antibody (BG7716) and anti-VEGF was well-tolerated and improved best-corrected vision and optical coherence tomography parameters. This was one of the first efforts to use dual-action targeting of both VEGF and Ang2. (Chakravarty U, et al. ARVO E-Abstract 4718)

Another anti-angiogenic, VEGF-independent compound presented at ARVO, SH-11037, in combination with aflibercept, inhibited human retinal endothelial cell proliferation more than either treatment alone, suppressed CNV lesions *in vivo* and appeared to act synergistically. (Sulaiman R, et al. ARVO E-Abstract 1108)

A key objective of intravitreal therapy is to minimize the number of injections without compromising efficacy. One study examined this using staged combination anti-VEGF therapy (ranibizumab and/or bevacizumab) with a sustained-release corticosteroid (Ozurdex, Allergan) and optional laser treatment. One-year results in 90 subjects indicated that staged combination therapy was effective in treating retinal vein occlusion and related cystoid macular edema, with fewer injections needed over one year. Additionally, results indicated that disease severity was related to more frequent injections, that treating ischemia may enhance early disease stabilization and that early treatment of RVO before the development of CME might potentially halt disease progression and prevent complications. (Cikatricis P, et al. ARVO E-Abstract 4154)

A multicenter clinical trial of 106 patients with vitreomacular adhesion or vitreomacular traction investigated the safety and efficacy of Allegro Ophthalmics’ synthetic anti-angiogenic and vitreolytic oligopeptide, Luminate. Patients with VMA are at risk for progression to VMT and its potential consequences: retinal edema; bleeding; optic nerve damage; visual impairment and blindness. Sixty-five percent of patients treated...
with the highest dose of Luminate achieved release of VMA or VMT by day 90, compared to 10 percent in the placebo group. Pharmacological treatment of VMA or VMT could reduce the risks associated with surgical intervention (pars plana vitrectomy). (Kappermann B, et al. ARVO E-Abstract 1809) Another VMT study of 113 subjects compared three non-surgical treatments, C3F8 gas, SF6 gas and intravitreal ocriplasmin, with follow-up of more than six months. C3F8 gas injection showed superior VMT release rates compared to SF6 and IVO treatments. (Steinle N, et al. ARVO E-Abstract 1806)

Dry AMD is the most common type of macular degeneration and, unfortunately, there are no pharmacological treatments currently available for it. In one study, however, a prosthetic implant placed within regions of geographic atrophy in late-stage dry AMD patients achieved successful integration of artificial (central) and natural (peripheral) vision. Surgeons implanted the Argus II electronic epiretinal prosthesis in four patients with subfoveal GA that severely affected their central vision. At follow-up (0.2 to 5.6 months), all of the patients showed central visual function elicited by the implant. (Stanga P, et al. ARVO E-Abstract 3733) In a related approach, surgeons implanted a prosthesis in three patients with advanced retinitis pigmentosa. After one year, this suprachoroidal-transretinal stimulating prosthesis elicited phosphenes in all three patients. Researchers observed the greatest improvements in visual tasks in patients with the electrode array implanted closer to the fovea centralis. (Fujikado T, et al. ARVO E-Abstract 5203)

In another study, investigators used quantitative spectral-domain OCT to develop a predictive model of GA designed to identify regions where GA is likely to appear in the future. They used scanning data to develop a statistical model that may eventually be used in clinical care, and as a biomarker for drug efficacy and device studies. (Leng T, et al. ARVO E-Abstract 1802)

**Presbyopia**

Current estimates project that around 1.8 billion people will be affected by presbyopia by 2050. With this staggering statistic, it’s not surprising that the condition was a dominant topic at this years’ ARVO. Treatments currently available for presbyopia include the use of reading glasses, contact lenses or refractive/ intraocular lens surgery. Lens wear is the most widely used option for treatment, despite the fact that lenses can have a limited field of view and/or cause severe distortion, the latter of which can cause discomfort or dizziness when wearers use different parts of the lens for various visual tasks. Although pharmaceutical therapies have been explored, thus far all of them have been limited in their treatment of the condition and have had some undesirable adverse effects.

Since presbyopia is a condition associated with aging in which the eyes lose their ability to adjust their focal length in order to produce focused images of near objects on the retina, one study investigated several important lens parameters in an attempt to further understand the role of the lens in accommodation. (Martinez-Enriquez E, et al. ARVO E-Abstract 1380) More precise estimates of geometrical parameters of the whole lens may be important for providing better IOL selection and customization of premium presbyopia correction solutions.

Presbyopic patients are not able to accommodate to see near objects but usually exhibit almost intact convergence and near-pupil response capabilities. Researchers capitalized on these characteristics by designing a device in which the optical power of optoelectronic lenses was driven by the size of the subject’s pupils. (Montpean J, et al. ARVO E-Abstract 1816)

In a controlled experimental setting, this system was successful in providing real-time focused images for objects placed at a variety of distances for presbyopic subjects.

Another group proposed a different approach to lens design for presbyopia treatment through a new design concept: harmonic diffractive liquid crystal lenses. (Guoqiang L, et al. E-Abstract 1818) Today, switchable electro-optic LC lenses offer a possible solution for presbyopia by overcoming the shortcomings of current therapies. However, developing LC lenses with high optical quality is difficult to achieve, since LC lenses can’t provide the aperture and power needed for spectacle lenses. This group demonstrated that harmonic diffractive LC lenses can accomplish vision correction that’s not possible with conventional diffractive LC lenses, thereby providing a promising new therapy for the correction of presbyopia.

**Allergy and Dry Eye**

Although it’s more of a niche market now at ARVO, the allergic conjunctivitis session remains near and dear to our therapeutic hearts.

The prominent role of the interleukins in allergy was the subject of several presentations. IL-33 was shown to have a significant role in an animal model of ragweed conjunctivitis. The discovery of type 2 innate lymphoid cells in the lacrimal glands prompted one group to investigate whether these cells were responsible for the IL-33 and eosinophil infiltration seen in their allergic model. It turns out that the lacrimal gland isn’t the reservoir of these cells, since excision of the glands didn’t alter the course of the IL-33 mediated ragweed con-
The roles of the adaptive immunity and innate lymphoid populations were also studied in a mouse model of chronic and severe allergic inflammation. Immuno-phenotyping of the innate lymphoid population in conjunctival cells identified predominantly CD45+, CD3-, B220-, CD11b- and GR-1 cells. As clinical signs of ocular allergy intensified, the collective number of these cells increased more than fivefold. All three of the innate lymphoid populations within this pool, which included Tbet+, GATA3+ and RORγt+ cells, appeared to increase in the conjunctiva by differing amounts.

In conjunctival impression cytology samples from vernal keratoconjunctivitis and normal subjects, three- to twentyfold increases in RNA expression were demonstrated in Th2 cytokines (IL-4, -5, -9, -13, -23), chemokines (CCL13, -18, -24 and others), and adhesion molecules. Many others were downregulated, including the cytokine precursors activating enzyme caspase 1, and toll-like receptor 5. Researchers tested Nasapaque for the relief of nasal and ocular itching induced by allergen exposure in the Ora Allergen Biocube chamber. Positive results provided further evidence of the neuronal nasal-ocular reflex for ocular itching. (Gomes P, et al. ARVO E-Abstract 305) Similar cross-talk was shown by a high, 92-percent incidence of itchy palate across five clinical trials using conjunctival allergen challenge, with 38 percent of subjects experiencing moderate to severe symptoms. (Schoemmell E, et al. ARVO E-Abstract 310) Using this same technology, Ocular Therapeutix researchers compared the pharmacokinetics of cyclosporine to Restasis in a canine model, (Smoot D, et al. ARVO E-Abstract 423) and tested a similar technology using intravitreal hydrogel depot for sustained release anti-VEGF in a rabbit model. (Blizard C, et al. ARVO E-Abstract 1120)

Gap junctions, which are large, non-selective membrane channels connecting the cell cytoplasm to the extracellular milieu, were the subject of a mini-symposium at this year’s ARVO, with a focus on connexin 43 function in the cornea and retina. In the eye, hemichannels assemble to form a gap junction. The hemichannel has been referred to as a pathological pore, and is a key component in the inflammasome pathway during both its initiation and propagation. Under injury and disease conditions, both connexin 43 expression and hemichannel permeability are increased, and therapeutic connexin 43 modulation has resulted in sight-saving outcomes in humans with persistent trabeculectomy scarring or severe ocular surface burns. Along these lines, speakers at the mini-symposium discussed pathological roles of connexin hemichannels in ocular injury and their potential as intervention sites. Studies discussed during the mini-symposium employed a variety of models, including a rat cornea keratectomy model, a rabbit model of cellular chemotaxis in allergic tissue. (Sugita et al. ARVO E-Abstract 304)

Thermal imaging of the ocular surface. Subtle differences in temperature can provide clues to the stability of the tear film and the underlying etiology of dry eye. (Sundstrom C, et al. ARVO E-Abstract 2851)
trabeculectomy model, a bright light retinal injury model and a rat retinal ischemia reperfusion model, to demonstrate the general importance of this cell constituent. Data from these studies were correlated with ex vivo human donor tissue analysis and suggest that loss of vascular integrity may be a common component in ocular disease. We look forward to following the progress of hemichannel modulation as a therapeutic means of protecting the eye from injury in multiple pathologic settings.

Another common theme was recent advances in the science of aging, including studies of central nervous system neurodegeneration, age-related changes in the RPE, the influence of aging on the immune system, epigenetic changes with age and oxidative damage in the retina. Concepts discussed this year included autophagy and mitophagy, homeostatic processes that clean up degraded or damaged mitochondria and other cell components. These processes are key to neuronal health and can go awry and lead to autophagic “traffic jams” in diseases involving retinal degeneration such as AMD. (Kearniranta K. ARVO E-Abstract 1400)

A common theme at ARVO was recent advances in the science of aging, including oxidative damage to the retina.

Therapies impacting these age-related defects include SkQ1, a novel antioxidant that accumulates in mitochondria where it’s reduced and regenerated, making it a potentially effective target for the treatment of the many diseases of oxidative stress. In an anterior chamber paracentesis rabbit model, topical application of SkQ1 was also shown to significantly enhance corneal wound healing in vitro, through enhancement of cell proliferation and migration. (Wei Y, et al. ARVO E-Abstract 1255)

Dry-eye sessions featured several related themes: there was the ever-present interest in linking disease signs and symptoms, and a continued interest in understanding the underlying physiology responsible for dry-eye heterogeneity. Research explored markers and biomarkers of disease, including INF-γ, IL-1R and MyD88. (Downie L, et al. ARVO E-Abstract 404; Courson J, et al. ARVO E-Abstract 405) Others examined chemo- kinase and cytokine expression. (Kessel K, et al. ARVO E-Abstract 406)

The neural aspects of dry eye were a major topic, with many studies of anatomical and physiological changes in corneal nerve function and how these may impact dry-eye disease. In one study, hyperosmolar stress was shown to damage corneal nerve fibers, (Mizierska K, et al. ARVO E-Abstract 403) while a second study demonstrated a role for vitamin D deficiency in poor nerve function. (Deshmukh R, et al. ARVO E-Abstract 2854) Several presentations established the importance of TrpM8 and TrpV1, membrane sensors responsible for thermo-sensation, as potential players in the signaling pathways impacted by dry eye. (Rocha E, et al. ARVO E-Abstract 393; Song J.S. ARVO E-Abstract 416; Situ P, et al. ARVO E-Abstract 2849; Corcoran P, et al. ARVO E-Abstract 2873) In parallel to these studies were those examining thermal imaging techniques to quantify minute temperature changes in the tear film and their potential impact on evaporative dry eye. (Sundstrom C, et al. ARVO E-Abstract 2851; Li W, et al. ARVO E-Abstract 2850; Watson M, et al. ARVO E-Abstract 2858)

ARVO provides a unique, research-oriented perspective on the state of ophthalmic science, allowing us to explore the latest trends and refresh our perspective on current technology and therapy. It’s also a great opportunity to exchange ideas with colleagues and recharge our batteries. As the meeting came to an end, we were reminded again of why we’ve made this pilgrimage for the past 30 years. See you next year in Baltimore.

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Dr. Hollander is chief medical officer at Ora, and an assistant clinical professor of ophthalmology at the Jules Stein Eye Institute at the University of California, Los Angeles. Dr. Abelson may be reached at MarkAbelsonMD@gmail.com.

Familial Glaucoma Risk: Spreading the Word

One way to reduce vision loss from glaucoma is to make sure our patients understand that their relatives are at increased risk.

Constance O. Okeke, MD, MSCE, Norfolk, Va.

We all know that glaucoma is a worldwide problem that leads to blindness. We also know that it’s especially problematic because it’s asymptomatic in its early stages; up to 50 percent of people with glaucoma don’t realize they have it. And as numerous population-based studies have demonstrated, one of the greatest risk factors for glaucoma is a family history of the disease. That means that one of the most important things we can do to address the disease is help identify those individuals among the families of our patients so that steps can be taken to preserve their vision.

For that identification to happen, people need to hear the message about glaucoma from someone they can trust, relate to and approach. With that in mind, this article is my call-to-action for ophthalmologists, glaucoma specialists, optometrists and anyone else who is seeing patients with glaucoma. Here are some ways you can help ensure that your patients are educated about glaucoma and its hereditary component, and a few strategies you can share with patients to help them convey the information to their family members.

The Importance of Heredity

Genetic studies have suggested that more than 50 percent of glaucoma is familial. It’s very strongly hereditary, especially among siblings; the rate of glaucoma can be 10 times higher among individuals with a sibling who has glaucoma. For example:

• The Baltimore Eye Survey not only found that open-angle glaucoma was much more prevalent in African Americans than Caucasians, it also found that if there was a family history of glaucoma the risk of developing glaucoma was significantly higher. That risk was even higher within the African-American population, and was highest among siblings.

• A study of 2,500 African-American individuals being conducted at the Scheie Eye Institute in Philadelphia found that those with a family history of glaucoma were 3.5 times as likely to have glaucoma as those with no family history of the disease; the risk was even greater if it was a sibling that had glaucoma. A family history of glaucoma was also associated with more aggressive disease, a three-year-earlier onset and a greater likelihood of undergoing glaucoma surgery.

• Tasmanian studies also found that glaucoma occurs about three years earlier and was more severe when other members of the family had had the disease.

• The Barbados Eye Study looked at more than 1,000 relatives of about 200 glaucoma patients who were followed for nine or 10 years. Out of those relatives, about 23 percent who were examined had glaucoma. In fact, the researchers found that the second highest risk factor for developing glaucoma was glaucoma being part of the family history.

• The Rotterdam Eye Study in the Netherlands found that having a family history of glaucoma increased the risk of a family member having glaucoma ninefold.

All of this data shows that family history matters, so if you have a patient with glaucoma you will probably also find it in other family members. It’s likely that at least 15 percent of our glaucoma patients have at least one sibling who has glaucoma, and that individual may be totally unaware of the disease. In other words, our patients are linked to a population...
of individuals who are much more likely to have glaucoma than a random sample of people. That means we have an opportunity to reach out to a number of individuals who have glaucoma but don’t know it—without having to cast too wide a net.

Clearly this is an avenue worth pursuing. However, there are two practical problems: First, communication within families is often incomplete, making patient reports of family history somewhat unreliable, and making the sharing of information with other family members potentially awkward. Second, as physicians we tend to be pressed for time, making it seem like a daunting task to pursue this concern with most of our glaucoma patients.

**Intra-family Communication**

There’s not much question that the odds of a family member getting screened increase dramatically if that family member understands the nature of glaucoma and the fact that it runs in families. That makes it crucial to get the word out to our patients’ blood relatives. The problem is, even if we manage to educate each and every glaucoma patient, there are other obstacles to reaching family members.

In general, when patients are already being treated for glaucoma, the outlook for spreading the news is good. The Baltimore Eye Survey found that most patients who were in the system, diagnosed and being seen, knew a lot more about their family history of glaucoma than individuals who weren’t being treated. That suggests that when they were diagnosed they were educated about the family history component, and other family members had been willing to share their health histories. But someone who is newly diagnosed is most likely not aware of how glaucoma works, or any family history of the disease.

Another issue that relates to this is that not every family shares their health history. The Tasmanian glaucoma study found that nearly 30 percent of the time glaucoma patients didn’t realize that other family members did have glaucoma. Along these same lines, I did some research when I was a resident at Wilmer Eye Institute trying to target family members who were at risk for glaucoma. We asked glaucoma patients what they knew about glaucoma; then we asked if it was OK to call family members to find out how much they knew. Were they aware of their family’s positive history of glaucoma? Did they know that glaucoma can be hereditary? Had they ever been checked for glaucoma?

What we found was that in Baltimore, only 77 percent of the family members we spoke to knew our patient had glaucoma. And when other family members reported having glaucoma, only 61 percent of our patients knew about it. So there’s some level of disconnect within families when it comes to talking about a glaucoma diagnosis.

In addition, we found that there was a mental disconnect between the idea that glaucoma is hereditary and the reality that this means family members are at risk. When we talked to our patients who were aware that there is a hereditary component, 30 percent of them still didn’t think it was important to tell their family members about the diagnosis and ask them to get their eyes checked.

The bottom line is that educating patients about glaucoma being hereditary is often not sufficient to get them to spread the word. Patients may not make the connection that this means family members are also at risk; they may not be aware that other family members have already been diagnosed; and they may not bother to pass along the information to other family members who are at risk.
Better Educating Patients

All of this means that we have a critical role to play when patients come into the system, to educate them about the hereditary component of glaucoma and the fact that it runs in families, and to do as much as possible to get patients to spread the word and encourage family members to get screened.

Here are some strategies that will help ensure that your patient's family members get checked:

• **Make this a regular part of your discussion when a patient is diagnosed with glaucoma.** Many times my patients say, “Thank you so much for letting me know and giving me this information,” because they care about their family members and they don’t want them to go blind. This discussion gives them a sense of responsibility. It usually takes less than 60 seconds to have the conversation before you leave the room.

• **Don’t assume that patients will make the connection between glaucoma having a hereditary component and family members being at risk.** The reality is that we need to spell things out very clearly. We have to convey that it’s important for the patient to let the family know that some family members may be at risk of vision loss, and that they all should be checked regularly.

• **Suggest that patients make a point of asking family members if they have glaucoma.** The research mentioned above indicates that awareness of glaucoma in the family is not guaranteed. The only way is to ask. If there’s a family history of glaucoma, it may make a difference in how carefully our patients need to be followed, since those with a family history tend to have more aggressive disease. Asking about family health history also gives your patient a platform to spread the word about familial risk.

• **Frame the sharing of this information with family as a gift, not a burden.** Some family members may take the attitude that getting screened is like looking for trouble. Everything is fine, don’t make me seek out bad news. We need to make it clear to patients that glaucoma may have no symptoms at first, but the earlier glaucoma is caught, the easier it is to treat. Encouraging family members to get checked is a way to make sure they don’t lose vision, because once they do, they can’t get it back. Sharing this information with family members is potentially giving them the gift of sight, even if it feels like a burden to bring it up.

• When relatives come in with the patient, take the opportunity to talk to them about this. This is a chance to spread the word among the very group that’s at elevated risk. You could even suggest that they make an appointment to get screened while they’re in your office.

• **Get your staff to help spread the message.** Staff members who are aware of the patient’s diagnosis can help spread the message that family members should be screened.

• **Suggest that the patient mention this at family gatherings.** Often, this is a good opportunity not only to spread the word but to get valuable family health history information, when multiple family members are present and can contribute their knowledge.

• **Host your own screenings for the family members of your patients.** Consider hosting a once-a-year event at which you provide free screenings for family members of your glaucoma patients, perhaps during glaucoma awareness month, or World Glaucoma Week. Then, make sure your patients know about it. Offering a free special event may inspire people to get checked who would otherwise not bother. (And be sure to participate in community screenings, especially in areas with higher African-American populations, or environments with primarily elderly individuals.)

• **Partner with patients who have large family reunions.** If some of your patients have family reunions attended by a large number
of individuals, consider offering to arrange a free screening during the reunion.

- **Participate in programs that provide free care, such as the AAO Glaucoma EyeCare Program.** Having this option available removes a major roadblock for family members who aren’t insured.

- **Put up posters in your waiting area and exam rooms.** Even with my personal passion for this cause, the realities of a busy clinical practice often used to leave me feeling like I had failed to communicate the issue of glaucoma running in families as completely as I should have. We’re all trying to be efficient and make sure we get to the next patient in a timely manner, so it’s easy to forget to mention that family members are also at risk and should be getting checked for the disease.

To help remedy that, I worked with Alcon to develop two posters that address this issue; they can be put up in your waiting room and/or exam rooms. The hereditary posters (shown on p. 61 and 62) include statistics about glaucoma and how members of the family are at higher risk; they talk about how untreated glaucoma can lead to blindness, and how being screened is important.

I’ve found that having these posters in the office greatly increases the likelihood of a discussion about getting the family screened. Either the patient points out the poster and asks about it, or I see it and it reminds me to mention the subject before I leave the exam room. Sometimes I’m in the room with family members, and they see the poster and start the discussion.

Having the posters up has made a big difference in terms of getting family members to come in. I’ve even had patients request copies of the posters to put up in their workplace. (Your drug rep should be able to get the posters for you.)

- **If your glaucoma patient is young, suggest that younger family members be screened as well.** If your patient is younger—say, in his 40s or 50s—with moderate or worse glaucoma, I would definitely tell him to get his teenage kids checked. (I sometimes treat glaucoma patients as young as 6 years old.) If the primary patient is diagnosed in the late 60s or later, I would suggest having family members in their 20s or older be screened. The age of diagnosis and stage of disease upon presentation gives you a sense of how aggressive the disease may be.

- **Provide your glaucoma patients with pamphlets or brochures addressing this.** It’s a lot to ask patients to remember all the details about why glaucoma is so problematic. A take-away brochure that can be passed along to family members can help ensure that complete information makes its way to those who are at risk. You can also provide links to videos that family members can watch. (We need to come up with more ways to encourage patients to spread the word, even if they have mixed feelings about starting the conversation with family members themselves.)

- **Join my campaign to make sure family members get screened.** There’s a lot that we can do to make sure this population of at-risk individuals doesn’t sneak under the radar. Many of the strategies I’m suggesting here are very simple, fast and free; we don’t have to do anything heroic. Meanwhile, these small steps could have a major impact on the disease. I think if we encourage physicians across the nation and around the world to pursue this, we can definitely reduce the number of people with glaucoma who remain undiagnosed (currently estimated at 50 percent).

Because of the nature of the doctor-patient relationship, we have a significant opportunity to educate patients about glaucoma. For the patient, the message is most likely to be heard if it comes from you. For the family member, the message is most likely to be heard if it comes from your patient. Hearing this from a family member can be much more motivating than hearing it from a public service announcement; people actually will make the effort to get checked.

Please join me and make a commitment to reaching your patients’ family members and encouraging them to get screened. We can definitely be more aggressive and creative about telling our patients how important it is for them to spread the word and urge family members to get checked. I’m already working with a number of individuals and organizations to further this cause. If a significant portion of eye-care professionals also make a commitment, we can have a major impact on reducing the number of undiagnosed individuals with glaucoma.

Dr. Okeke is an assistant professor of ophthalmology at Eastern Virginia Medical School in Norfolk, Va., and a glaucoma specialist and cataract surgeon at Virginia Eye Consultants. You can reach her at iglaucoma@gmail.com.


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**References:**

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How to Handle LASIK Rip-offs

Postop tears, displacements and other flap trauma can result in complications and poor vision.

Walter Bethke, Managing Editor

While some prospective LASIK patients worry about investing in a procedure from one of a few unethical businesses that might not deliver on all their promises, LASIK surgeons have to deal with a rip-off of a different stripe: Postop tears, displacements and other sorts of flap trauma that can result in complications and poor vision. In this article, surgeons share pearls from actual cases of flap trauma they dealt with in their practices.

Case-study Pearls

Surgeons say you can take different tacks depending on such factors as whether the trauma recently occurred or occurred further in the past, as well as whether the cornea is torn or not and the extent of epithelial ingrowth in the interface.

• The intact flap. York, Pa., surgeon Denise Visco encountered a patient, 10 years postop after her LASIK, who had bent over her tomato garden and ran her eye into a plant stake. “She immediately had pain, loss of vision and foreign body sensation,” Dr. Visco recalls. “Since I wasn’t in the office that day, she saw my optometrist, who did nothing to it, including touching the flap. The next day someone else saw her, but still didn’t touch the flap. I informed the eye-care providers that they have to touch the flap to properly examine it, which I promptly did with a sterile cotton-tipped applicator, and saw that it moved. In the short, six-hour period between the injury and her first visit to our office, the epithelium had already begun to grow into the interface. Then, between that visit and the second one at which I saw her, she was actually 50-percent re-epithelialized underneath the flap on the corneal bed.”

In such a case, Dr. Visco says it’s helpful to put the patient under the laser microscope and thoroughly debride everything. “I didn’t use any alcohol or mitomycin, but I made sure I removed all of the epithelium on the base of the flap,” she says. “I also scraped the epithelium off of the underside of the flap. I removed any epithelium that looked thick and loose, even on top of the flap. Then, I went around the edge of the flap and removed approximately 0.5 to 1 mm of epithelium around the edge of the ocular side of the flap. I think removing the epithelium from around the edge like this gives the flap a head start for adhering; it creates a delay before it reaches the edge of the flap. The stronger the bond between the flap and the bed, the less chance the epithelium can slip under.”

After that, Dr. Visco had to deal with another common issue with flap trauma: striae. “When I went to put the flap back down, it had folds and wasn’t very adherent to the bed,” she says. “In response, I used a trick that I had learned years ago from a colleague: Create a mixture that’s 50 percent BSS and 50 percent water and instill it onto the eye. As the flap absorbs the mixture, it will swell and some of the...
Denise Visco, MD

In trauma, epithelial ingrowth is a concern. Surgeons will scrape everywhere, including the underside of the flap, to remove it.

wrinkles will disappear. Also, it makes the tissue surfaces of the flap and the bed more tacky, so the flap will adhere to the bed better. I then let the flap dry for about five minutes, placed a bandage contact lens and watched it daily. The patient was lucky: She went from counting fingers at presentation to hand motions/CF after I finished my intervention. After two weeks she saw 20/50 and had no epithelial ingrowth, and, after a year, she now sees 20/20.

The medications during that postop period are important, and surgeons say they're similar to a postop LASIK medication regimen, but more intense. “I treated her with Zymaxid antibiotics, topical steroids, Pred Forte q1h, and Medrol dose packs with a double taper.” Dr. Visco explains. “I also gave her some gabapentin for discomfort. I wanted her on more oral steroid than just a single pack, so I kept the dose the same but doubled the time. So, instead of taking six doses on day one, five on day two, et cetera, she took six doses on day one, six on day two, five on day three, five on day four and so on. It’s easier to do this than to give the patient a big bottle of 5 or 10 mg pills and say, ‘Take six for four days, five for four days, et cetera.’”

Greensboro, N.C., surgeon Karl Stonecipher agrees that choice of post-repair medicine is important in these patients. “For antibiotics, I prefer vancomycin because it covers the majority of staph species, and I’ll use Polytetra or gentamicin because it will usually make up the difference for me in my neck of the woods,” he says. “I wouldn’t fault anyone if they used a fluoroquinolone, though. I wouldn’t use an antibiotic that has a lot of mucoadhesives, however, because if it’s too sticky it can be challenging to work with when a contact lens is in place. If the patient has an injury from an organic cause, such as a branch or bush, I would also strongly consider putting him on the antifungal natamycin in addition to the antibiotic. In terms of steroids, I’ll use a long-term steroid, probably with a month taper. In many cases I’ll use Pred Forte rather than Durezol because of the latter’s mucoadhesives, but if the flap is ripped off and it’s bare sclera I’ll typically use Durezol. I’ll also watch the patient’s pressure for pressure-induced stromal keratitis. Note that it can be challenging measuring pressures in these post-flap trauma cases, and you can’t measure it early on because you have them in a contact lens.”

**The torn flap.** The situation changes when the patient’s flap is torn by the trauma, surgeons say. This was the type of scenario faced by Bradenton, Fla., surgeon Cathleen McCabe when a 60-year-old patient, who had undergone LASIK monovision 10 years prior, had a trauma similar to Dr. Visco’s: Three months before seeing Dr. McCabe, the patient was gardening and suffered an injury to her left eye from a steel rod. Unlike Dr. Visco’s case, however, this patient had developed an infection in the injured eye, which healed after antibiotic treatment but which the patient said left a “wrinkle in the cornea.” The vision in the left eye, which had been left a little myopic by the monovision LASIK, was 20/50 uncorrected, and 20/20-1 with correction. Upon examination, Dr. McCabe saw that the left eye’s flap was torn, and there was epithelial ingrowth, fixed folds and anterior stromal scarring.

“I consulted with colleagues, and was considering lifting the flap to remove the epithelium to see if the flap was salvageable,” says Dr. McCabe. “However, it didn’t look like it was. One of the tools I used that I found very helpful was anterior segment OCT. With it, I could see the disrupted corneal flap and that the scarring went deeper than the flap; it didn’t look salvageable on OCT.” (See image, above.)

While considering her options, one of the surgeons Dr. McCabe spoke to was William Wiley, MD, of Cleveland, Ohio. He told her about a patient with persistent epithelial ingrowth beneath his flap in which Dr. Wiley amputated the flap and then did a series of ORA intraoperative aberrometry readings to get the residual refractive error. “Dr. Wiley took an ORA reading pre-flap lift, then another through a bandage contact lens pre-lift,” Dr. McCabe recalls. “He then lifted the flap and took readings with and without the bandage contact lens to see if he could get a better reading with the contact lens in place and also to determine what the
effect of the contact lens was. He then amputated the flap and performed an excimer PRK at 60 percent of the ORA refractive-error reading, and the patient did well." Dr. McCabe says that most surgeons, though, will manage the ingrowth and flap issues as best they can, then wait for refractive stability before performing any refractive procedure. Many surgeons will use adjunctive mitomycin-C.

In Dr. McCabe’s case, the patient actually moved away to Michigan; a surgeon there amputated the flap, sutured amniotic membrane over the area and waited for it to heal. Now, the patient sees 20/25 uncorrected.

Dr. Stonecipher says that flap removal is a more viable option these days than in the early days of LASIK. “In many late flap traumas, a referring surgeon will have already tried to repair them,” he says. “I’ve had trauma cases referred to me after they’ve tried to suture the flap down but it’s got epithelial ingrowth and melting of the flap edges. When I was dealing with such a case years ago, Jack Holladay told me to just take the flap off. I objected, thinking the patient would be +10 D, but Dr. Holladay said that if it was a femtosecond flap, it most likely will be all right. It turns out that the older, microkeratome flaps were cut in such a configuration that, if they were removed, the patient might end up hyperopic. But the femtosecond flap is planar and doesn’t leave the patient hyperopic if it’s removed. So, you can remove the flap, let it re-epithelialize under a bandage contact lens—usually 15 to 25 mm in diameter—and the patient usually does well. You can then typically perform a PRK enhancement. However, in some cases, the previous creation of a 100- to 120-µm flap leaves the patient with 300 to 400 µm of residual stromal bed, which may not be enough for PRK if the patient has a large refractive error. At that point, you have to either put him in a refractive element such as glasses or contact lenses, or perform a refractive lensectomy to make him whole again.”

Dr. Stonecipher consults for Alcon, Allergan and B + L. Dr. McCabe consults for Alcon. Dr. Visco has no financial interest in the products discussed.
Identifying the Pachychoroid Phenotype

Sub-segmenting the choroid using novel imaging modalities may lead to a better understanding of macular diseases.

Rosa Dolz-Marco, MD, PhD, New York City, Kunal K. Dansingani, MA, FRCOphth, Omaha, Neb., and K. Bailey Freund, MD, New York City

New technologies in ophthalmic imaging, particularly enhanced-depth imaging optical coherence tomography and swept-source OCT, have overcome some of the limitations of flood photography and visible spectrum imaging, thereby allowing us to better visualize tissues deep to the retinal pigment epithelium.¹,²

The pachychoroid spectrum exemplifies our ability to harness these new modalities in order to understand better the choroidal changes that underlie central serous chorioretinopathy and to define an expanded phenotype through recognition and classification of several macular disorders that share a similar choroidal phenotype.

Features

The pachychoroid phenotype features: 1) reduced fundus tessellation on clinical examination or white light photography; 2) relatively increased choroidal thickness, which may be focal or diffuse; 3) pathological dilation of outer choroidal (Haller) vessels, referred to as “pachyvessels”; and 4) loss of choriocapillaris and Sattler layers overlying pachyvessels.³,⁴ Pachyvessel morphology has been further characterized by en face structural OCT, which also provides valuable data on the topological variations in choroidal thickness.⁵

Pachychoroid pigment epitheliopathy (PPE) refers to a precursor or forme fruste of CSC in which focal or multifocal RPE changes are seen without evidence of concurrent or preceding neurosensory detachment.³ The RPE changes occurring in PPE resemble those

Figure 1. Pachychoroid pigment epitheliopathy in a 61-year-old. A. Color fundus image. B. Fundus autofluorescence. C. Structural optical coherence tomography.
frequently detected in the fellow eye of patients presenting with unilateral neurosensory detachments due to CSC. Like those with CSC, eyes with PPE also exhibit choroidal hyperpermeability on indocyanine green angiography co-localized with pachychoroid features. Failure to recognize these choroidal changes can result in these patients being assigned other diagnoses such as early AMD, atypical pattern dystrophy, retinal pigment epitheliitis or punctate inner choroidopathy (See Figure 1).

The location and distribution of RPE changes in PPE are spatially co-localized with the distribution of pachyvessels, particularly where they lie in close proximity to the Bruch’s membrane-RPE complex, due to focal loss of the overlying choriocapillaris and Sattler layer volume.

Central serous chorioretinopathy is a well-described disorder in which serous pigment epithelial detachments and serous neurosensory detachments occur at the posterior pole in the absence of inflammatory features. Subretinal fluid accumulates via focal or diffuse leaks at the level of the RPE, which are demonstrable by fluorescein angiography, and is therefore thought to originate in the choroid. OCT shows the smooth, convex profile typical of serous pigment epithelial detachments and that the subretinal fluid is often detected above a serous PED showing leakage on FA (See Figure 2).

In the acute form, CSC is usually self-limited with good visual recovery. However, a subset of patients may experience either a chronic or remitting-relapsing course with a range of complications and compromised visual acuity. Chronicity is often characterized by RPE changes occurring in the distribution of subretinal fluid. These RPE changes may be non-specific or may have a gravitating morphology that is best visualized on fundus autofluorescence. OCT may also show outer retinal changes, such as thickened photoreceptor outer segments and ellipsoid zone disruption associated with chronic subretinal fluid. Complications of chronic CSC may include outer retinal atrophy, neovascularization, cystic macular degeneration and bullous retinal detachment.

Pachychoroid Neovasculopathy

Pachychoroid neovasculopathy (PNV) refers to the presence of type 1 neovascularization in eyes with a pachychoroid phenotype. Patients developing PNV are typically a decade or two younger than patients developing neovascular age-related macular degeneration. Pachychoroid neovasculopathy also differs from neovascular AMD in that it occurs in eyes with thicker choroids and pachyvessels with absent or minimal drusen. Type 1 neovascularization in PNV often develops insidiously and may arise in eyes with PPE which have not previously
exhibited frank subretinal fluid (See Figure 3).

In PNV, hyperfluorescence on FA due to type 1 neovascularization may be ill-defined and difficult to detect when it occurs within a background of RPE changes related to chronic CSC. With ICGA, late-staining plaques representing type 1 neovascularization may be obscured from detection by choroidal hyperpermeability. Cross-sectional OCT is often helpful in showing findings suggestive of sub-RPE neovascularization including shallow irregular RPE elevations containing material of heterogeneous but intermediate reflectivity. These shallow, irregular PEDs have frequently been shown by OCT angiography to harbor neovascular tissue. The finding of shallow irregular PEDs in pachychoroid eyes on structural OCT is therefore considered to be a sensitive sign for neovascularization.

Polypoidal choroidal vasculopathy was first described by Lawrence Yannuzzi, MD, and associates in terms of polypoidal vascular lesions, thought to occur in the inner choroid, that predispose to exudative and hemorrhagic complications. In the initial description, PCV was described by the ICGA appearance of the polypoidal lesions. Subsequent studies with OCT localized both the polypoidal lesions and their feeding vascular networks below the RPE, but above Bruch’s membrane, suggesting that polypoidal lesions originate from type 1 neovascular tissue (See Figure 4).

The factors predisposing to the development of polypoidal lesions in some patients with type 1 neovascularization remain unclear, but the fact that PCV occurs with greater frequency in patients with Asian and African ancestry suggests some genetic basis. Although PCV is traditionally studied and treated as a variant of AMD, it often occurs in eyes that lack drusen and in patients who are younger than those with typical AMD. Additionally, in both Asian and Caucasian patients with polypoidal lesions, cross-sectional and en face OCT frequently show choroidal features more consistent with the pachychoroid phenotype than with AMD. Patients with a pachychoroid phenotype, type 1 neovascularization and associated polypoidal lesions might be better classified as having a
PUSHING THE FUTURE OF EYE CARE FORWARD

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pachychoroid spectrum entity than a variant of AMD.11

In summary, multimodal imaging has enabled an enhanced appreciation of specific choroidal features associated with CSC and an expanded spectrum of macular disease including PPE, PNV and a subset of PCV. Previously, patients presenting with these entities were difficult to diagnose (PPE), or classified as having a variant of AMD.12

The definition of the pachychoroid phenotype continues to evolve as we sub-segment the choroid using novel imaging modalities and tools. With an enhanced appreciation regarding the significance of pathologic choroidal changes in a variety of macular diseases, research may now expand to explore new disease mechanisms with potential impact on therapeutic strategies and visual outcomes. REVIEW

Dr. Dolz-Marco is an international medical retina fellow at Vitreous Retina Macula Consultants of New York and junior researcher at Unit of Macula, Institute of Health Research, University and Polytechnic Hospital La Fe in Valencia, Spain. Dr. Dansingani is an assistant professor of ophthalmology and visual sciences at Trihlese Eye Institute, University of Nebraska Medical Center, in Omaha, Neb. Dr. Freund is a retina specialist at Vitreous Retina Macula Consultants of New York; clinical professor of ophthalmology at the New York University School of Medicine; and on staff at New York Presbyterian Hospital, Manhattan Eye Ear & Throat Hospital, and Lenox Hill Hospital. Contact Dr. Freund at kbfnyf@aol.com.

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Brightening the future of eye care
Dear Resident Program Director and Coordinator,

We would like to invite you to review the upcoming 3rd-Year Resident Programs for 2016 in Fort Worth. The programs offer a unique educational opportunity for third-year residents by providing the chance to meet and exchange ideas with some of the most respected thought leaders in ophthalmology. The programs are designed to provide your residents with a state-of-the-art didactic and wet lab experience. The programs also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

Sincerely,
Postgraduate Healthcare Education

Third-Year Resident Programs 2016:

**August 19-20**
Fort Worth, TX
Course Director:
Mitchell Weikert, MD

**September 9-10**
Fort Worth, TX
Course Director:
Anthony Arnold, MD

**September 16-17**
Fort Worth, TX
Course Director:
Tommy Korn, MD

For more information:
Visit the registration site above or
Email: dholmes@postgradhealthed.com
Call: Denette Holmes 866-627-0714

Courses are restricted to 3rd-year residents enrolled in an ophthalmology resident program and within their third year 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.

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

Credit Designation Statement
This activity has been approved for AMA PRA Category 1 Credit™.

Supported by an unrestricted independent medical educational grant from

Review of Ophthalmology®
Citing strides made by women in ophthalmology in the traditional metrics of professional advancement, researchers from a half-dozen U.S. and one Australian medical center sought to test one more: professional ties to industry as another potential means of career advancement, recognition and income.

They found that women make up a minority of ophthalmologists with professional industry relationships, and the average woman partnering with industry earns less than her male colleagues.

The observational, retrospective study used data from the Centers for Medicare & Medicaid Services to track payments to ophthalmologists by biomedical companies. Primary outcome measures were percentage of representation of women vs. men overall and in industry research, consulting, speaking roles, royalties and licenses, grants, services other than consulting and honoraria.

As of 2013, 4,164 (19.5 percent) ophthalmologists were women, and of 1,204 ophthalmologists analyzed for industry payments, 176 (4.2 percent) women had industry ties compared with 1,028 (6 percent) men ($p<0.001$). Mean payments to women were $14,848 compared with $30,513 for men ($p=0.004$), and median payments to women were $8,750 compared with $5,000 for men ($p=0.005$). Women remained underrepresented among ophthalmologists receiving industry payments for research 10.4 percent; consulting 15.7 percent; honoraria 12.6 percent; industry grants 12 percent; royalties and licenses 4.6 percent; and faculty/speaker roles 11.1 percent.

The group reported that the reasons are multifactorial and could not be determined by their study.

Reddy AK, Bounds GW, Bakri SJ, Gordon LK.

**NFL Thinning May Predict Functional Decline**

Progressive retinal nerve fiber layer thinning is predictive of detectable functional decline in glaucoma and underscores the significance of detecting progressive RNFL thinning to initiate or augment treatment for glaucoma patients, based on a long-term prospective study by researchers from China and San Diego. They recommend that progressive RNFL thinning may be an outcome measure for clinical trials.

For five years they followed 139 primary open-angle glaucoma patients (240 eyes), with RNFL imaging and visual field testing at about four-month intervals. Progressive RNFL thinning was determined by event analysis (GPA) and trend analysis (TPA) of serial registered RNFL thickness maps. VF progression was detected according to the Early Manifest Glaucoma Trial and pointwise linear regression criteria. Hazard ratios for predicting VF progression were calculated by Cox proportional hazard modeling, with progressive RNFL thinning as a time-dependent covariate. Main outcome measures were the hazard ratios of the VF progression. The specificity of GPA/TPA for detection of RNFL changes was determined by the proportion of eyes with significant RNFL thinning/thickening in 25 normal subjects followed weekly for eight consecutive weeks and the proportion with significant RNFL thickening in the glaucoma group.
A total of 65 (27.1 percent) and 117 eyes (48.8 percent) had progressive RNFL thinning based on GPA and TPA, respectively, and 50 (12.5 percent) and 39 eyes (16.3 percent) had VF progression per the EMGT and PLR criteria, respectively, during follow-up. Eyes with progressive RNFL thinning had lower VF survival estimates and a faster decline of visual field index than eyes without. Progressive RNFL thinning predicted the development of VF progression with HRs of 8.44 (95 percent confidence interval) (EMGT criteria) and 5.11 (PLR criteria) for TPA and 3.95 (EMGT criteria) and 3.81 (PLR criteria) for GPA after controlling for baseline covariates. The specificities of GPA and TPA were 100 percent (83.4 to 100 percent) in the normal group and 81.7 percent and 84.2 percent, respectively, in the glaucoma group.

Yu M, Lin C, Weinreb RN, Lai G, Chiu V.

Shift Workers, Sleep-Deprived May be at Risk for CSCR

Shift work or sleep disturbances may be risk factors for central serous chorioretinopathy, according to researchers in France and Switzerland.

Their prospective case-control series recruited 45 patients with active CSCR and 40 age- and sex-matched controls. All patients completed a questionnaire on previously described risk factors and working hours, as well as an Insomnia Severity Index. Mean age in study subjects was 44 ±9 years, and 43 ±10 years in controls.

By use of multivariate analysis, shift work (odds ratio [95 percent confidence interval]: 5 [1.2 to 20.4], p=0.02; steroid use (OR: 5.5 [1.1 to 26.2], p=0.03); and recent psychological stress (OR: 15.3 [4.1 to 54.5]; p<0.001) were found to be independently associated with CSCR.

Bousquet É, Dhundass M, Lehmann M, Rothschuld PR.

Study Reports Daily Vesneo Results vs. B.I.D. Timolol

POLLO, a Phase III study by Bausch + Lomb, has demonstrated significantly greater intraocular pressure-lowering effect by latanoprostene bunod (LBN) ophthalmic solution 0.024% (Vesneo, B+L) administered every evening compared with timolol maleate 0.5% twice daily in subjects with open-angle glaucoma or ocular hypertension.

The Phase III, randomized, controlled, multicenter, double-masked, parallel-group clinical study included 420 subjects with OAG or OHT; they were randomized (2:1) to a three-month regimen of LBN 0.024% q.p.m. or timolol 0.5% one drop b.i.d. IOP was measured at 8 a.m., 12 p.m. and 4 p.m. of each postrandomization visit (week two, week six and month three).

The primary efficacy endpoint was IOP in the study eye measured at each of the nine assessment time points. Secondary efficacy endpoints included the proportion of subjects with IOP ≤18 mmHg consistently at all nine time points and the proportion of subjects with IOP reduction ≥25 percent consistently at all nine time points.

At all nine time points, the mean IOP in the study eye was significantly lower in the LBN 0.024% group than in the timolol 0.5% group (p≤0.002). At all nine time points, the percentage of subjects with mean IOP ≤18 mmHg and the percentage with IOP reduction ≥25 percent were significantly higher in the LBN 0.024% group versus the timolol 0.5% group (mean IOP ≤18 mmHg: 22.9 percent vs. 11.3 percent, p=0.005; IOP reduction ≥25 percent: 34.9 percent vs. 19.5 percent, p=0.001). Adverse events were similar in both treatment groups.

Weinreb R, Slovis I, Vithalw J, Liewmann, J.

Transplant Techniques Have Their Own Advantages

Researchers in Brazil compared two surgical procedures for the treatment of corneal thinning: lamellar corneal transplantation—reported to be efficient, but whose results can be jeopardized by allograft rejection, opacification or high astigmatism—and amniotic membrane transplantation—considered a good alternative, but not as resistant as LCT and subject to tissue being reabsorbed after surgery.

The prospective, randomized, interventional and comparative study included 19 consecutive patients with corneal thinning over six months. All were examined before transplant surgery and then repeated days one, seven, 15, 30, 90 and 180; ultrasound biomicroscopy was performed before and then 30, 90 and 180 days after surgery to assess corneal thinning.

Herpes simplex infection was the main cause of corneal thinning (nine eyes), followed by surgery (cataract, glaucoma, five cases), and one each for rheumatoid arthritis, chemical burn, perforating trauma, previous band keratopathy treatment and Stevens-Johnson syndrome. Although all patients showed significant increase in final thickness in the area of thinning, it was higher in those submitted to LCT at 180 days postoperatively. Regardless of the surgical technique, all patients showed epithelialization. Patients undergoing AMT showed an 89-percent decrease in neovascularization. Final corrected distance visual acuity was better in patients submitted to AMT.

Cornea 2016;35:438-44.

de Farias CC, Allemann N, Gomes JÁ.
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 viewing the video, participants should be able to demonstrate a method to minimize the use of ultrasonic energy during phacoemulsification.

CME Accredited Surgical Training Videos Now Available Online: www.MackoolOnlineCME.com

Richard Mackool, MD

Video Overview:
Utilizing high vacuum, removal of a 2+ nuclear cataract is accomplished without ultrasound.

Episode 6: “Phacoaspiration of a Nuclear Cataract in a 78 Year Old Patient”
Surgical Video by: Richard J. Mackool, MD

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

Credit Designation Statement
IAHB designates this live activity for a maximum of .25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
ThromboGenics announced that the Food and Drug Administration has approved a new already-diluted formulation of its Jetrea (ocriplasmin). The new formulation of Jetrea offers the additional benefit of eliminating the current preparatory dilution steps prior to injection. At the point of administration into the eye, the strength, potency, composition and pharmaceutical form of the already-diluted formulation remain identical to the currently available formulation after dilution.

Jetrea is approved in the United States for the treatment of symptomatic vitreomacular adhesion, an age-related progressive, sight-threatening condition that may lead to visual distortion, decreased visual acuity and central blindness.

ThromboGenics, which is commercializing Jetrea in the United States, plans to launch the already-diluted formulation of Jetrea in the first half of 2017. More information is available at thrombogenics.com.

Efficient In-Office Procedures

Reliance Medical Products and Haag-Streit USA announced the new I-OPS In-Office Procedure System at the American Society of Cataract and Refractive Surgery in May. Developed in collaboration with Christopher Riemann, MD, of the Cincinnati Eye Institute, I-OPS is an ergonomically optimized instrument delivery system that allows physicians to perform injections and other minor in-office procedures much more efficiently. I-OPS eliminates wasted movements, which saves time and improves patient flow, as well as patient safety and comfort, the company says.

Physicians can now perform a multitude of procedures without the need for an assistant or the need to turn around and reach for supplies, increasing productivity and efficiency. By eliminating the need for an assistant during procedures, the physician’s staff is also able to focus on documentation and other productive tasks.

The modular I-OPS System features a durable tray with space for up to nine interchangeable inserts. The ability to organize and set up procedures beforehand brings consistency and standardization to procedures. Physicians can keep a hand, and their attention, on the patient, reducing patient stress levels and increasing their comfort.

The I-OPS tray and accessory kit come with two syringe holders, deep and shallow cups and one each of a dropper bottle holder, twist bottle holder and gel pack holder. If the physician prefers to customize his system, inserts are available for purchase in any combination a la carte.

The basic I-OPS arm fits almost any manufacturer’s stand pole and is easy to move to swing out of the way of patients. It also comes with Reliance Medical Products standard one-year warranty. For information, visit haag-streit-usa.com/IOPS, or view the I-OPS video on YouTube.

AngioVue Retina from Optovue

Optovue announced the immediate availability of AngioVue Retina, a proprietary imaging system that provides retina specialists with a non-invasive, dyeless way to quickly visualize blood flow in the retina.

AngioVue Retina is configured with...
essential optical coherence tomography angiography and OCT features designed specifically for retinal practices to allow adoption of OCT and OCTA into the clinical workflow with minimal disruption.

Optovue's AngioVue Retina provides retinal specialists with the ability to quickly visualize the presence or absence of retinal vessels and assess new information about the microvasculature with extraordinary detail. This information may be integrated with other diagnostic imaging results to form a complete picture of a patient's disease state and their treatment options.

The company also announced its new DualTrac Motion Correction for use with both the AngioVue and AngioVue Retina systems, a two-level approach to correcting motion artifacts resulting from patient movement. The first level provides real-time correction for rapid eye movements, blinking or eye drifting. The second level occurs during imaging post-processing and corrects smaller levels of motion distortion. This combined approach results in robust motion correction for patients who have trouble directing their focus on a central point during an eye exam, which is essential for high quality OCTA imaging.

For information, visit optovue.com.

Moria Adds to Punch Portfolio

Moria has extended its portfolio in purely endothelial graft preparation with new Single-Use Donor Vacuum Guarded Punches to safely assist corneal surgeons and/or eye-bank practitioners in the preparation of purely endothelial graft following the SCUBA (“no touch”) technique: the Guarded Punch.

Its 350-µm guarded blade is designed to make a non-penetrating trephination of the Descemet's membrane all around 360° without any hinge, so delamination becomes an easy process.

Guarded punches are currently available in six diameters: 9.5- and 10.0-mm: for a peripheral scoring; 7.5-, 7.75-, 8.0-, 8.5-mm to finalize the purely endothelial graft size.

With the new guarded punches, just one press scores Descemet's membrane, creating a clean, 360-degree stromal incision to easily find a cleavage plane for the consecutive delamination.
Career Opportunities

Bassett Healthcare Network
Bassett Medical Center

Bassett Healthcare Network, a progressive health care network in central New York and major teaching affiliate of Columbia University, is seeking a General Ophthalmologist to join a busy ophthalmology department based in the lovely village of Cooperstown. Glaucoma experience a plus!

Bassett Healthcare Network is an integrated health care system that provides care and services to people living in an eight county region covering 5,600 square miles in upstate New York. The organization includes six corporately affiliated hospitals, as well as skilled nursing facilities, community and school-based health centers, and health partners in related fields.

**KEY BENEFITS OF THIS POSITION:**
- Opportunities exist for both research and teaching if interested.
- Currently there are specialists in retina, cornea, pediatrics and oculoplastics.
- The support staff is well trained and experienced in both the clinic and operating room.
- Group employed model with competitive salary
- Comprehensive benefit package, including but not limited to medical, dental, CME, relocation assistance and paid malpractice insurance

Bassett Medical Center is located in Cooperstown, New York, a beautiful resort village on Otsego Lake. Home to the National Baseball Hall of Fame and Museum, the Glimmerglass Opera Company, and the Fenimore Art Museum, the area also boasts many cultural and four season recreational advantages including theater, music, museums, golf, sailing, hiking, and skiing.

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phone: 607-547-6982; fax: 607-547-3651; email: debra.ferrari@bassett.org
or visit our web-site at www.bassettopportunities.org
The Rick Bay Foundation
for Excellence in Eyecare Education
www.rickbayfoundation.org

Support the Education of Future Healthcare & Eyecare Professionals

About Rick
Rick Bay served as the publisher of The Review Group since 1991.

To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.

To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

Scholarships are awarded to advance the education of students in both Optometry and Ophthalmology, and are chosen by their school based on qualities that embody Rick’s commitment to the profession, including integrity, compassion, partnership and dedication to the greater good.

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The Rick Bay Foundation for Excellence in Eyecare Education
(The Rick Bay Foundation for Excellence in Eyecare Education is a nonprofit, tax-exempt organization under section 501(c)(3) of the Internal Revenue Code.)
Dear Fellowship Program Director and Coordinator,

We would like to invite you to review the upcoming 2016 Glaucoma Fellowship Program in Fort Worth at the Renaissance Worthington hotel. The program offers a unique educational opportunity for fellows by providing the chance to meet and exchange ideas with some of the most respected thought leaders in glaucoma. The Glaucoma Fellows Program is designed to provide your fellows with a state-of-the-art didactic and wet lab experience. The program also serves as an opportunity for your fellows to network with fellows from other programs.

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

Sincerely,
Postgraduate Healthcare Education

Course Director:
Kuldev Singh, MD
Stanford, CA

Wet Lab Director:
Douglas J. Rhee, MD
Cleveland, OH

Faculty:
Lee Alward, MD
Donald Budenz, MD
Ronald Fellman, MD
Brian Flowers, MD
Steven Gedde, MD
Dale Heuer, MD
Shan Lin, MD
Eydie Miller-Ellis, MD
Louis Pasquale, MD
Harry Quigley, MD
Arthur Sit, MD
George Spaith, MD
Janey Wiggs, MD, PhD

For More Information & to Register:
www.revophth.com/2016cseglaucoma

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.

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

Credit Designation Statement
Amedco designates this live activity for a maximum of 13.50 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
A woman’s recent decrease in vision follows on an earlier hospital admission for headaches and optic disc edema.

**Presentation**

A 38-year-old Hispanic woman presented to the Wills Eye Hospital emergency department with a four-day history of left greater than right eye decreased vision.

Recent medical history revealed admission to the Neurology service at our hospital two months prior for headaches and optic disc edema in the right eye. Inpatient ophthalmology consultation was obtained, and an evaluation for typical and atypical causes of optic nerve edema was recommended. Serologic workups for Lyme, sarcoidosis, syphilis and tuberculosis were negative. Magnetic resonance imaging of the brain, orbit and cervical and thoracic spine was negative for optic nerve enhancement or demyelinating lesions. Chest radiography showed no infiltrates or lymphadenopathy. Lumbar puncture for infectious and autoimmune etiologies of optic nerve edema returned normal results. She had been empirically diagnosed with idiopathic optic neuritis and treated with three days of high-dose IV methylprednisolone with resolution of her symptoms. She was discharged on an oral taper of prednisone with gradual return of her symptoms bilaterally after she had completed the taper. Review of systems during her current presentation revealed left-sided headache, malaise, nausea, vomiting, photophobia and neck pain.

**Medical History**

Past medical history revealed migraines, hypothyroidism and anxiety. Social history was unremarkable. Family history disclosed a sister with sarcoidosis.

The patient’s medications included oxycodone for chronic lower back pain, as well as carisoprodol, nortryptiline, clonazepam and levothyroxine.

**Examination**

Corrected visual acuity was 20/30 in the right eye and count fingers at three feet in the left eye. A relative afferent pupillary defect was present in the left eye. Intraocular pressure was 12 mmHg in both eyes, and extraocular motility was full. Confrontation visual fields were full in the right eye but could not be assessed in the left eye due to decreased visual acuity. Anterior segment exam showed 2+ temporal conjunctival injection, fine keratic precipitates and 1+ anterior chamber cell and flare, as well as trace vitreous cell in both eyes.

Dilated examination of the right eye showed faint retinal pigment epithelial mottling and optic disc edema. In the left eye, a multi-lobed serous retinal detachment involving the macula and multiple serous retinal detachments temporal and nasal to the macula (See Figure 1).

**What is your differential diagnosis? What further workup would you pursue? Please turn to p. 76**
Diagnosis, Workup and Treatment

Spectral-domain optical coherence tomography demonstrated a small amount of subretinal fluid in the right eye and extensive subretinal fluid with RPE undulation, inflammatory membranes and ellipsoid zone disruption in the left eye (See Figure 2). Fluorescein angiography demonstrated early patchy choroidal filling, pinpoint areas of hyperfluorescence in the posterior pole, pooling of fluorescein in areas of detachment in the left eye and disc hyperfluorescence in both eyes (See Figure 3).

These findings, in addition to the patient's systemic complaints, were suggestive of the acute uveitic stage of Vogt-Koyanagi-Harada (VKH) disease (also called VKH syndrome). Therapy was initiated with 60 mg of prednisone a day. Ten days after initiating therapy, macular OCT (See Figure 4) showed resolution of subretinal fluid with improved foveal contour in both eyes. The ellipsoid zone continued to show breakage and disappearance, and the patient's visual acuity in both eyes remained unchanged at this early follow-up.

Discussion

VKH disease is a granulomatous, multisystem, autoimmune disorder affecting tissues with large amounts of melanin pigment, including the eyes, meninges, skin and auditory system. It most commonly affects more heavily pigmented individuals, including Hispanics, Asians, Native Americans, Middle Easterners and Asian Indians. The exact mechanism and sensitizing factor in patients with VKH disease is unknown, although evidence suggests a T-lymphocyte-mediated process against an unidentified antigen of melanocytic cells.1-4

In 2001, an international consensus panel published a revised list of diagnostic criteria for designating VKH...
disease as “complete” or “incomplete” based on the spectrum of manifestations seen at the time of presentation. Ophthalmic criteria include bilateral ocular involvement with no history of ocular trauma or surgery and no evidence suggestive of other ocular disease entities. Systemic manifestations are divided into neurologic/auditory findings including meningismus, tinnitus or cerebrospinal fluid pleocytosis and integumentary findings including alopecia, poliosis or vitiligo. “Complete” VKH disease requires all of the above criteria to be met at some point in the patient’s disease course, while “incomplete” VKH disease requires all ophthalmic criteria as well as either neurologic/auditory or integumentary findings. The panel also allowed for a designation of “probable” VKH disease in patients who met the above ocular criteria in the absence of systemic signs or symptoms.

The clinical course of VKH disease typically follows four stages. The prodromal stage mimics viral illness and can include headaches, tinnitus, neck stiffness, nausea and hearing loss.

This is followed three to five days later by the acute uveitic stage that can last for several weeks and includes signs of panuveitis, optic disc swelling and choroiditis with exudative retinal detachments. The chronic vasculitic stage gradually develops and manifests as depigmentation of the skin and uvea. During the chronic vasculitic stage, there may be recurrent episodes of uveitis known as the chronic recurrent stage that lead to vision-threatening complications including cataracts, glaucoma, choroidal neovascular membranes and subretinal fibrosis.

Ophthalmic imaging can be utilized to further characterize clinical findings. Fluorescein angiography most frequently features early patchy choroidal filling, early pinpoint hyperfluorescence in the posterior pole, disc hyperfluorescence and subretinal pooling of fluorescein in areas of exudative retinal detachment. Features on OCT that distinguish VKH from other causes of serous retinal detachment include folds of RPE, fluctuation of the internal limiting membrane and subretinal septa disrupting the photoreceptor layer. In chronic forms of VKH, the RPE can show signs of thickening and breakage, as well as disappearance of the cone outer segment tip (COST) line or ellipsoid zone. The use of OCT with enhanced-depth imaging can provide better visualization of the choroid, which can be thickened in acute-phase and chronic-recurrent phase VKH patients.

Treatment of VKH in the acute phase is generally with high-dose corticosteroids, either orally or intravenously. No prospective trials have compared different routes of systemic corticosteroid treatment, but a retrospective interventional case series involving 48 patients initially treated with oral or intravenous corticosteroids with an oral taper found no difference in treatment effect between the two groups. Initial doses of corticosteroid are typically 1 mg/kg/day with a maximum adult oral dose of 60 to 80 mg/day and a maximum maintenance dose of ≤10 mg/day. Steroids are typically slowly tapered over a period of six months or more as tolerated. Timothy Lai, MD, and colleagues studied duration of treatment in a retrospective review of 35 patients and found that patients who received less than six months of oral corticosteroid were more likely to experience recurrence and have a worse visual outcome. Immunomodulatory agents can be initiated in cases of disease incompletely controlled on corticosteroids or if disease severity necessitates the use of unacceptable high doses of corticosteroid.

In conclusion, VKH is a multi-system inflammatory disorder with bilateral ocular involvement most commonly manifesting as multifocal exudative retinal detachments due to diffuse choroiditis. Depending on the timing of presentation, there are a variety of neurologic, auditory and integumentary manifestations. The syndrome progresses through numerous stages, and in the acute phase it is most commonly treated with high-dose corticosteroids. Later, a chronic recurrent stage can develop that may require treatment with long-term immunomodulatory agents. The diagnosis is one of exclusion after an appropriate clinical and laboratory evaluation for other uveitic processes that could mimic the inflammatory ocular findings. Due to the systemic nature of VKH, the presence of bilateral panuveitis and features of choroiditis should prompt a detailed review of systems to avoid a delay in treatment.

**References**

The Ophthalmology Innovation Summit (OIS) series has expanded with a third affiliate meeting at the American Society of Retina Specialists (ASRS) on August 8th in San Francisco. This half-day summit will focus on innovative treatments for retinal diseases.
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1. Internal Data; 2016.

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