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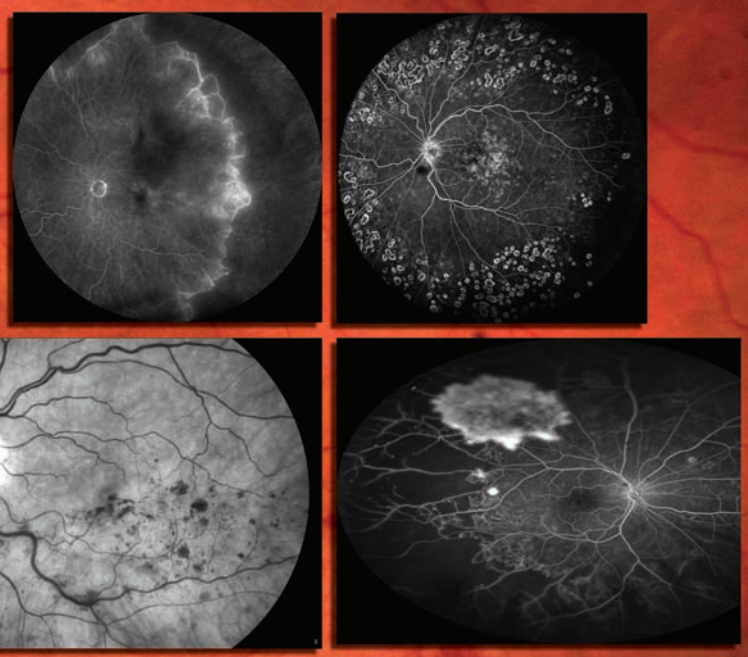

ANNUAL *RETINA* ISSUE

The Devil's in the Distant Details *P. 26*

Maximizing the Benefits of Anti-VEGF *P. 30*

Increasing Options to Treat Vein Occlusion *P. 40*

Also Inside:

The Critical Driver of Success: Physician Time P. 22

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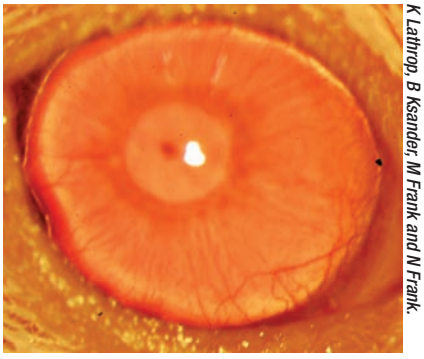
REVIEW NEWS
Volume XXI • No. 8 • August 2014

Researchers: First Tissue Grown From Adult Human Stem Cell

Boston researchers have identified a way to enhance regrowth of human corneal tissue to restore vision, using a molecule known as ABCB5 that acts as a marker for hard-to-find limbal stem cells. This work, a collaboration between the Massachusetts Eye and Ear/Schepens Eye Research Institute, Boston Children's Hospital, Brigham and Women's Hospital and the VA Boston Healthcare System, provides promise to burn victims, victims of chemical injury and others with damaging eye diseases. The research, published this week in *Nature*, is also one of the first known examples of constructing a tissue from an adult-derived human stem cell.

Limbal stem cells help maintain and regenerate corneal tissue. Their loss due to injury or disease is one of the leading causes of blindness. In the past, tissue or cell transplants have been used to help the cornea regenerate, but it was unknown whether there were actual limbal stem cells in the grafts, or how many, and the outcomes were not consistent.

In this study, researchers were able to use antibodies detecting ABCB5 to zero in on the stem cells in tissue from deceased human donors and use them to regrow anatomically correct, fully functional human corneas in mice.



K Lathrop, B Ksander, M Frank and N Frank.

A restored functional cornea following transplantation of human ABCB5-positive limbal stem cells to limbal stem cell-deficient mice. Transplants consisting of human ABCB5-positive limbal stem cells resulted in restoration and long-term maintenance of a normal clear cornea, whereas control mice that received either no cells or ABCB5-negative cells failed to restore the cornea.

"Limbal stem cells are very rare, and successful transplants are dependent on these rare cells," says Bruce Ksander, PhD, of Mass Eye and Ear, co-lead author on the study with postdoctoral fellow Paraskevi Kolovou, MD. "This finding will now make it much easier to restore the corneal surface. It's a very good example of basic research moving quickly to a translational application."

ABCB5 was originally discovered in the lab of Markus Frank, MD, of Boston Children's Hospital, and Natasha Frank, MD, of the VA Boston Healthcare System and Brigham and

FDA Approval for Ozurdex 0.7 mg for Select DME Cases

The Food and Drug Administration approved Allergan's Ozurdex (dexamethasone intravitreal implant) as a new treatment option for diabetic macular edema in adult patients who have an artificial lens implant or who are scheduled for cataract surgery. Ozurdex is a sustained-release biodegradable steroid implant that demonstrated long-term efficacy without the need for monthly injections.

DME currently impacts more than 560,000 Americans. The Ozurdex implant uses the proprietary and innovative Novadur solid polymer delivery system—a biodegradable implant that releases medicine over an extended period of time—to suppress inflammation, which plays a key role in the development of DME.

The FDA approval of Ozurdex for this indication is based on the MEAD (Macular Edema: Assessment of Implantable Dexamethasone in Diabetes) study. MEAD includes two multicenter, three-year, sham-controlled, masked, randomized clinical studies assessing the proportion of patients with 15 or more letters improvement in best-corrected visual acuity from baseline. The most common adverse events in the studies included cataracts and elevated intraocular pressure. An increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles.

"DME is a complicated disease to treat," said Pravin Dugel, MD, clinical associate professor of ophthalmology at the Keck School of Medicine at the University of Southern California, managing partner of Retinal Consultants of Arizona, and clinical investigator in the MEAD clinical trial. "Ozurdex provides long-term improvement of DME without the need for monthly injections, which helps these patients who are also managing the other conditions common with diabetes."

The Ozurdex implant is already indicated for the treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion and for the treatment of noninfectious uveitis affecting the posterior segment of the eye.

Women's Hospital, co-senior investigators on the study, as being produced in tissue precursor cells in human skin and intestine. In the new work, using a mouse model developed by the Frank lab, they found that ABCB5 also occurs in limbal stem cells and is required for their maintenance and survival, and for corneal development and repair. Mice lacking a functional ABCB5 gene lost their populations of limbal stem cells, and their corneas healed poorly after injury.

"ABCB5 allows limbal stem cells to survive, protecting them from apoptosis [programmed cell death]," said Markus Frank. "The mouse model allowed us for the first time to understand the role of ABCB5 in normal development, and should be very important to the stem cell field in general," said Natasha Frank.

Markus Frank is working with the biopharmaceutical industry to develop a clinical-grade ABCB5 antibody that would meet U.S. regulatory approvals. "A single lab cannot do a study like this," said Natasha Frank, also affiliated with the Harvard Stem Cell Institute. "It integrates genetics, knockout mice, antibodies, transplantation—a lot of technical expertise that we were lucky came together in a very nice way."

Cataract Surgery Pays Dividends in Alzheimer's Patients

Cataract surgery for people with Alzheimer's disease and other dementias not only improves vision but can slow decline in cognition and improve quality of life for both people with the disease and their caregivers, according to clinical trial results reported in July at the Alzheimer's Association International Conference 2014 in Copenhagen, Denmark.

"This study supports the Alzheimer's Association view that people with dementia retain, and benefit from, full health-care treatment," said Maria Carrillo, PhD, Alzheimer's Association vice president of medical and scientific relations. "Too common attitudes such as, 'There's no need for extra care' or 'Why put them through all of that' are not justified and are bad medical practice."

"Appropriate thoughtfulness and restraint are necessary when considering surgery or other procedures for people with Alzheimer's or another dementia. However, we should not assume that medical procedures cannot be pursued or are too risky. As these new results show, improving sensory abilities, for example, can provide benefits in a variety of ways—for people with Alzheimer's and also for their caregivers from whom unnecessary burden can be lifted," Dr. Carrillo said.

At AAIC 2014, Alan J. Lerner, MD, of Case Western Reserve University and University Hospitals Case Medical Center and colleagues reported interim results from an ongoing clinical trial to determine the effects of cataract removal on several measures of visual ability, cognitive measures, and quality of life in people with dementia. Study participants are recruited from dementia and ophthalmology clinics at University Hospitals Case Medical Center and MetroHealth Medical Center in Cleveland, and are divided into two groups: 1) immediate surgery following recruitment and; 2) delayed or refused surgery. Vision and cognitive status, mood and capability to complete daily activities are evaluated at baseline and six months after recruitment, or six months after surgery.

Preliminary analysis of results from 20 surgical and eight non-surgical participants showed that the surgical group had significantly improved visual acuity and quality of life, reduced decline in memory and executive functioning, and improvements in behavioral measures compared with the non-surgical group. Levels of perceived burden for caregivers of people in the surgical group also showed improvement.

"These preliminary results indicate that improved vision can have a variety of benefits for people with dementia and their loved ones, both visual and non-visual," said Dr. Lerner. "Our findings need to be verified in a larger study, but they suggest the need to aggressively address dementia co-morbidities such as vision-impairing cataracts, while balancing safety and medical risks."

"If the results hold up, it will significantly affect how we treat cataracts in

Expanded Approval for B + L Victus

Bausch + Lomb has received 510(k) clearance from the FDA for the Victus Femtosecond Laser Platform for laser-assisted lens fragmentation during cataract surgery.

The fragmentation procedure, which follows a capsulotomy, uses the femtosecond laser to split the cataractous lens into sections. This is followed by phacoemulsification for cataract removal. he Victus platform offers a number of different lens fragmentation patterns depending on the cataract grade and user preference.

"Academic research has shown that cataracts pre-treated with lens fragmentation can require less phacoemulsification energy for removal," said Y. Ralph Chu, MD, founder and director of the Chu Vision Institute, Bloomington, Minn. "In lower grade cataracts, we have seen up to a 50-percent reduction in the phaco energy required to remove the lens following lens fragmentation with the laser, compared with standard phaco."

B + L has been installing Victus platforms in leading surgery centers globally since it received CE mark in November 2011 and the FDA clearances in July 2012. It is now one of the only femtosecond lasers in the U.S. with clearance for the creation of a corneal flap in patients undergoing LASIK surgery, anterior capsulotomy during cataract surgery, penetrating arcuate cuts/incisions in the cornea and laser-assisted lens fragmentation during cataract surgery.

individuals with dementia. Other interventions to offset sensory loss—including vision and hearing—may help improve quality of life for people with dementia and their caregivers," Dr. Lerner added.

According to the Alzheimer's Association, a person with dementia has the right to any medical treatment available. People with the disease may require longer courses of some treatments such as rehabilitative therapies compared to people with intact cognition. Therapies that may be of benefit should not be discontinued because a person with Alzheimer's has failed to make progress as the same rate as someone without the disease.

> *"If the results hold up, it will significantly affect how we treat cataracts in individuals with dementia."*
> *— Alan J. Lerner, MD*

Making medical decisions about treatment remains the right of the person with Alzheimer's until he or she no longer has the cognitive capacity to understand the decision. At that time, medical decisions are made by the person's surrogate. The Alzheimer's Association recommends that preferences about medical treatment and decisions should be addressed early in the disease process through the execution of advance directives. Absent an advance directive, the surrogate decision maker should be guided by the values and any expressed wishes of the person with Alzheimer's disease. REVIEW

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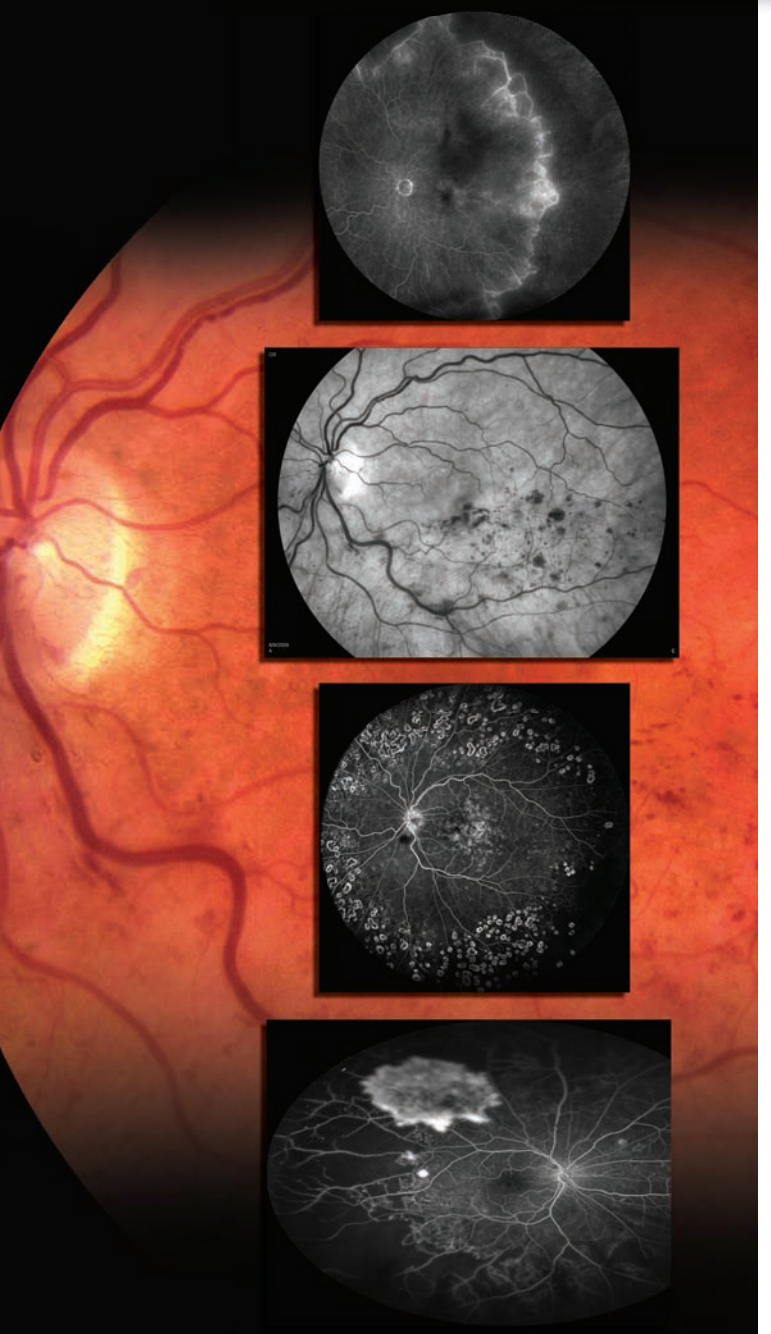

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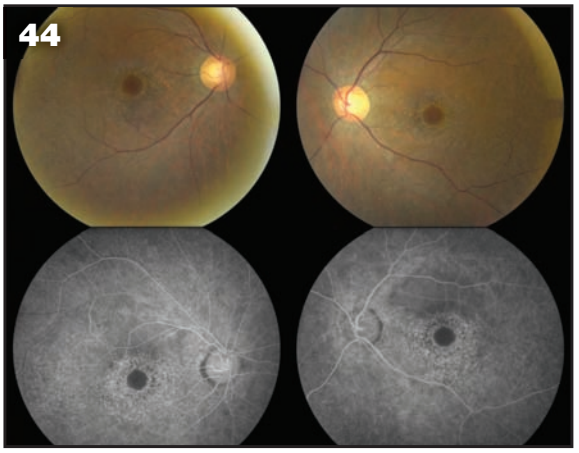

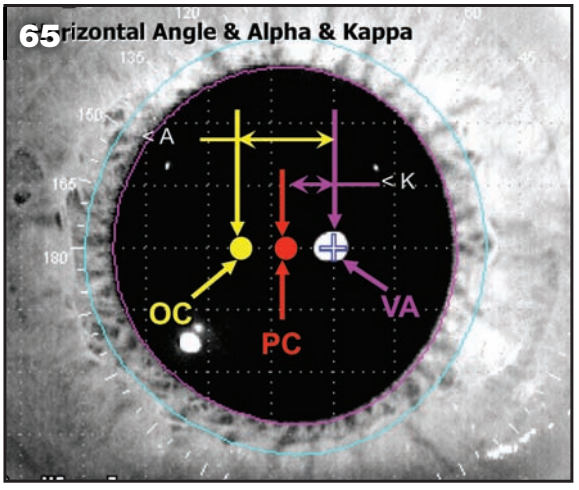

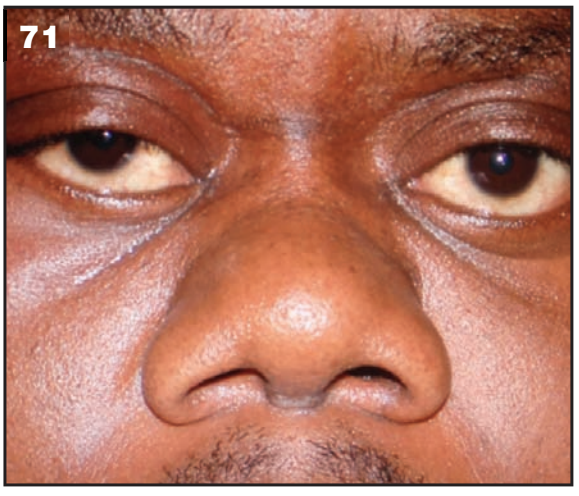

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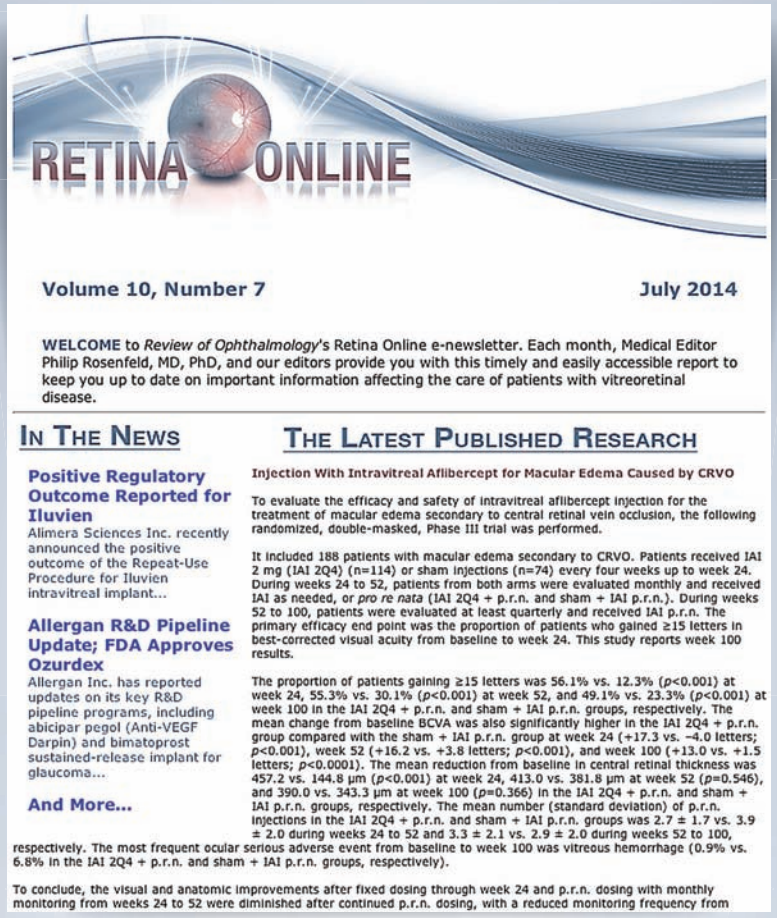

RETINA ONLINE

Volume 10, Number 7 July 2014

WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

IN THE NEWS

Positive Regulatory Outcome Reported for Iluvien
Alimera Sciences Inc. recently announced the positive outcome of the Repeat-Use Procedure for Iluvien intravitreal implant...

Allergan R&D Pipeline Update; FDA Approves Ozurdex
Allergan Inc. has reported updates on its key R&D pipeline programs, including abicipar pegol (Anti-VEGF Darpin) and bimatoprost sustained-release implant for glaucoma...

And More...

THE LATEST PUBLISHED RESEARCH

Injection With Intravitreal Aflibercept for Macular Edema Caused by CRVO

To evaluate the efficacy and safety of intravitreal aflibercept injection for the treatment of macular edema secondary to central retinal vein occlusion, the following randomized, double-masked, Phase III trial was performed.

It included 188 patients with macular edema secondary to CRVO. Patients received IAI 2 mg (IAI 2Q4) (n=114) or sham injections (n=74) every four weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed, or *pro re nata* (IAI 2Q4 + p.r.n. and sham + IAI p.r.n.). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI p.r.n. The primary efficacy end point was the proportion of patients who gained ≥15 letters in best-corrected visual acuity from baseline to week 24. This study reports week 100 results.

The proportion of patients gaining ≥15 letters was 56.1% vs. 12.3% (p<0.001) at week 24, 55.3% vs. 30.1% (p<0.001) at week 52, and 49.1% vs. 23.3% (p<0.001) at week 100 in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + p.r.n. group compared with the sham + IAI p.r.n. group at week 24 (+17.3 vs. −4.0 letters; p<0.001), week 52 (+16.2 vs. +3.8 letters; p<0.001), and week 100 (+13.0 vs. +1.5 letters; p<0.0001). The mean reduction from baseline in central retinal thickness was 457.2 vs. 144.8 µm (p<0.001) at week 24, 413.0 vs. 381.8 µm at week 52 (p=0.546), and 390.0 vs. 343.3 µm at week 100 (p=0.366) in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean number (standard deviation) of p.r.n. injections in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups was 2.7 ± 1.7 vs. 3.9 ± 2.0 during weeks 24 to 52 and 3.3 ± 2.1 vs. 2.9 ± 2.0 during weeks 52 to 100, respectively. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9% vs. 6.8% in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively).

To conclude, the visual and anatomic improvements after fixed dosing through week 24 and p.r.n. dosing with monthly monitoring from weeks 24 to 52 were diminished after continued p.r.n. dosing, with a reduced monitoring frequency from

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New Tech, New Patients Drive Systemic Change

We're reaching the point where real-world effects of the 2010's Affordable Care Act, Obamacare, can start to be documented. In the months since it began to kick in, the ACA is starting to produce some real evidence of its impact.

This month the *New England Journal of Medicine* reported that 10.3 million Americans gained health coverage this year, and that the percentage of uninsured patients fell from 21 percent in September 2013 to 16.3 percent in April 2014. What appears not to have materialized yet is the inundation of the health-care system by the newly insured that many experts had foreseen.

But the system is still preparing for it in a variety of ways, such as expanded use of technology and expanding treatment privileges, that represent major changes from traditional care.

• The Federation of State Medical boards has drafted a model law that would ease the way to multiple-state licensure, enabling treatment by videoconference and online.

• CMS rulemakers have proposed a new telemedicine payment policy to extend Medicare reimbursement to wellness and behavioral health visits.

• Medical insurers WellPoint and Aetna this month began offering patients, by next year as many as 8 to 10 million of them, the ability to have "e-visits" with doctors, virtual visits in which the physicians may prescribe drugs, in some states.

• Missouri enacted legislation this month that allows medical school graduates to become assistant physicians, with no residency, to practice primary care and prescribe drugs in underserved or rural areas of the state, with oversight of a licensed physician.

• An *Annals of Internal Medicine* study this month offers an expanded role for nurse practitioners (including writing and changing prescriptions) in managing chronic diseases as an effective solution to the shortage of primary-care physicians. A new law this month in Kentucky for the first time allows similar independent privileges to nurse practitioners, following an established collaboration with a physician.

• Illinois enacted legislation aimed at bringing doctors and nurses out of retirement to help as volunteers in free medical clinics. The law allows retired health professionals to get volunteer licenses at no cost. The law waives fees for the first 500 volunteer licenses and then allows for a fee waiver or reduction. The law also applies to dentists, physician assistants and optometrists.

As the pressure points and demands of increased medical coverage become apparent, the system is changing in ways that not so long ago would not have been imagined.


Ocular Sealants and Glues in Review

A look at the ways ophthalmologists use sealants and glues, and where the newly approved ReSure sealant fits in.

Walter Bethke, Managing Editor

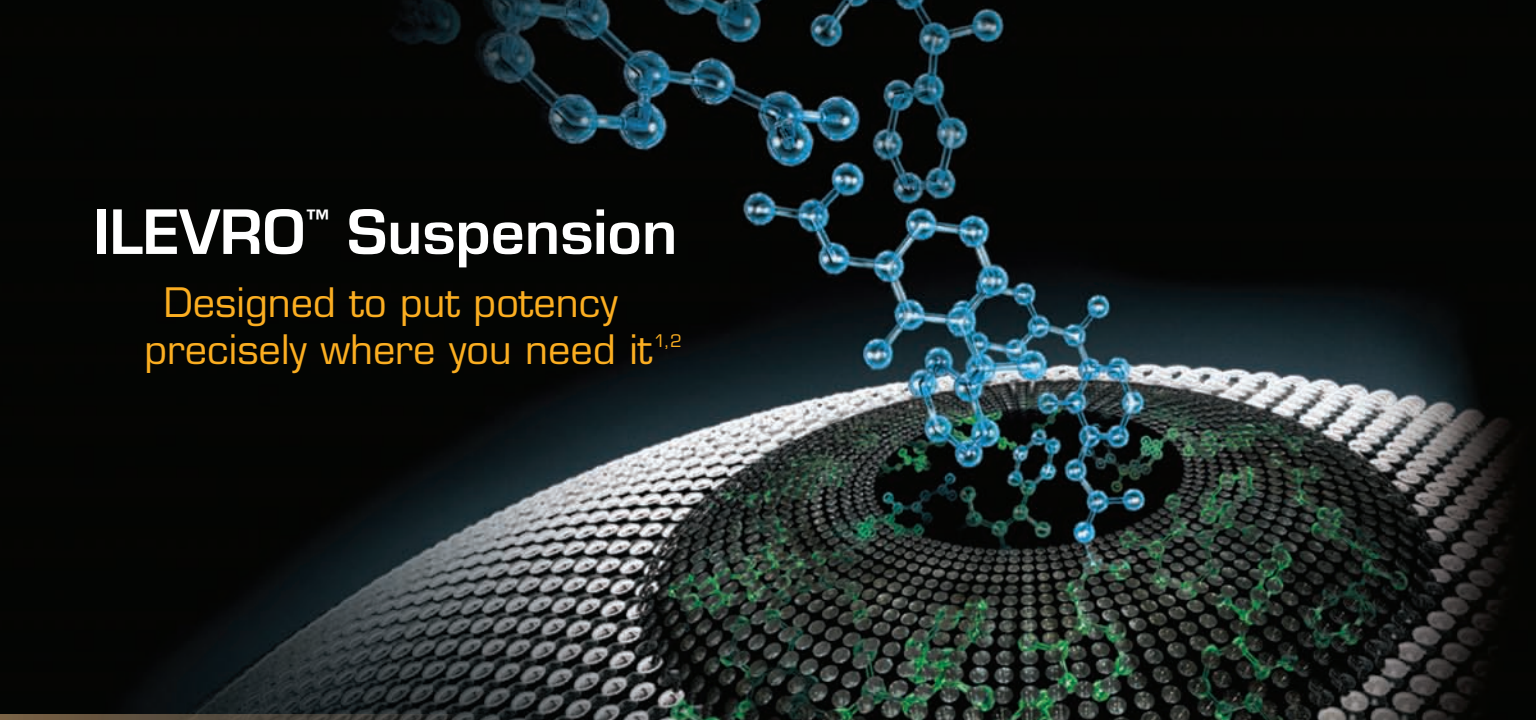
The use of synthetic glues and bioadhesives has made life simpler for a lot of surgeons, allowing them to secure ocular tissues or protect tissues from further damage from such pathologies as corneal perforations. Recently, ophthalmologists got another option in the sealant realm with the approval of ReSure Sealant (Ocular Therapeutix). Here's a review of the current glues and sealants, tips for their use, and new uses surgeons have been trying with them.

• ***Cyanoacrylate.*** Though not officially approved for use on the eye, cyanoacrylate has been used by ophthalmologists for more than 30 years. "The main indication for cyanoacrylate is the management of perforated corneal ulcers, both sterile and infectious," says Christopher Rapuano, MD, director of the cornea service at Philadelphia's Wills Eye Institute. "It works well for that indication. We also use it for ulcers where the cornea is very thin and might perforate in the next couple of days or weeks; we just fill it with glue and let it heal before it perforates. Since it's not FDA-approved, I have patients sign a consent form that states what we're doing and that it's not FDA-approved but it's a standard treatment."

Dr. Rapuano says that, when working with cyanoacrylate, controlling moisture in the area of operation is key. "Cyanoacrylate polymerizes as soon as it touches something like water, aqueous or saline," he explains. "So, if you have a perforation and aqueous is coming out, as soon as cyanoacrylate hits the aqueous it will solidify. This is good and bad. In the presence of moisture, it's good in that it will solidify pretty instantly. But if you have a dry divot and put down the glue, it will remain as a liquid for several minutes until the moisture around the glue polymerizes it. The danger is that, if it hasn't polymerized and you touch it with something like a Weck-Cel, it will start to polymerize as you're touching it, and you'll get this wick that comes off the glue. So, you have to be really patient and not touch any wet glue with either an instrument or a Weck-Cel. So, when I'm 95-percent sure it's polymerized, I'll flood it with saline or proparacaine so I'm sure it's polymerized. Also, you don't want to put a contact lens on it when it's in its liquid state because I've seen glue adhere to soft contact lenses. However, you almost always have to cover the polymerized cyanoacrylate with a soft contact lens because the surface is very rough and you don't want to cause the patient discomfort or have the lids poke at it with each blink and risk dislodging it."

Dr. Rapuano says it works very well for sterile perforations, but in infections it can be more challenging. "In infected perforations, the tissue tends to be mushier and the cyanoacrylate doesn't stick that well," he says. "Sometimes for sterile perforations it stays on for many months. In those cases you just have to keep changing the contact lens and following the patients. Once the cornea heals, the glue will pop off."

• ***Fibrin glue.*** This is a biologically derived tissue sealant (as opposed to the synthetic cyanoacrylate) that's indicated for use in controlling bleeding. Like cyanoacrylate, even though it's not specifically approved for ophthalmic surgeries, ophthalmologists have found several uses for it. "Fibrin glues such as Evicel, Tisseel and Artiss are used to secure tissue to the surface of the eye," says Dr. Rapuano. "Spe-



ILEVRO™ Suspension

Designed to put potency precisely where you need it[1,2]

ONCE-DAILY POST-OP

One drop should be applied once daily beginning 1 day prior to surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery[3]

Use of ILEVRO™ Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events[3]

INDICATIONS AND USAGE

ILEVRO™ Suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

Dosage and Administration

One drop of ILEVRO™ Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

IMPORTANT SAFETY INFORMATION

Contraindications

ILEVRO™ Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

Warnings and Precautions

- Increased Bleeding Time – With some nonsteroidal anti-inflammatory drugs including ILEVRO™ Suspension there exists the potential for increased bleeding time. Ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- Delayed Healing – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Corneal Effects – Use of topical NSAIDs may result in keratitis. In some 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.

  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.

  Use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.
- Contact Lens Wear – ILEVRO™ Suspension should not be administered while using contact lenses.

Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5 to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

For additional information about ILEVRO™ Suspension, please refer to the brief summary of prescribing information on adjacent page.

References: 1. Ke T-L, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation, II: In vitro bioactivation and permeation of external ocular barriers. *Inflammation*. 2000;24(4):371-384. **2.** Data on file. **3.** ILEVRO™ Suspension package insert.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO™ Suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of ILEVRO™ Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Use with Other Topical Ophthalmic Medications
ILEVRO™ Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

CONTRAINDICATIONS
ILEVRO™ Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

WARNINGS AND PRECAUTIONS
Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including ILEVRO™ Suspension, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ILEVRO™ Suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Delayed Healing
Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ Suspension, 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.

Corneal Effects
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 ILEVRO™ Suspension and should be closely monitored for corneal health. Postmarketing 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.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

Contact Lens Wear
ILEVRO™ Suspension should not be administered while using contact lenses.

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

Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased post-implantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO™ Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO™ Suspension during late pregnancy should be avoided.

Nursing Mothers
ILEVRO™ Suspension is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO™ Suspension is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of ILEVRO™ Suspension in pediatric patients below the age of 10 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Contact Lens Wear
ILEVRO™ Suspension should not be administered while wearing contact lenses.

Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

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

Shake Well Before Use
Patients should be instructed to shake well before each use. U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

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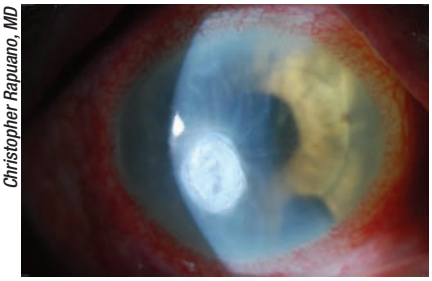
cifically, this takes the form of securing conjunctival tissue during pterygium surgery with conjunctival auto-grafts, and securing amniotic membrane tissue in pterygium surgery or another surgery where amniotic membrane is used to cover some abnormality or conjunctival defect."

An interesting evolving technique using fibrin glue was developed by Chennai, India, surgeon Amar Agarwal. In complicated cases in which an intraocular lens can't be fixated normally, Dr. Agarwal has built upon ideas first proposed by German surgeon Gábor Scharioth, MD, PhD. In Dr. Agarwal's glued-haptic technique, the surgeon first creates two partial-thickness, limbal-based scleral flaps 180 degrees apart. Then, the surgeon performs an anterior vitrectomy. With the help of an assistant, the surgeon externalizes the haptics through the sclerotomies, then tucks the ends of the haptics into a Scharioth intralamellar tunnel he creates with a 26-ga. needle at the location of the externalization. The surgeon then closes the scleral flaps over the externalized haptics with fibrin glue.[1]

"Fibrin glue solidifies at a different rate than cyanoacrylate," explains Dr. Rapuano, "so you have to get used to knowing how quickly you have to move before it's attaching things. Fibrin glue will begin to secure things after about 30 seconds to a minute. Though it takes 10 minutes before it's totally secure, it starts to polymerize pretty quickly."

• ***ReSure sealant.*** ReSure is made of a polyethylene glycol hydrogel, which is a different material from cyanoacrylate or fibrin glue, and is approved for the sealing of clear corneal incisions used in cataract removal/IOL implantation. It actually comes as two separate materials, a polyethylene glycol solution and a trilysine amine solution, which, when mixed together by the user, form the sealant. An applicator that comes in the ReSure kit is used to apply the mixture to the eye.



Christopher Rapuano, MD

Cyanoacrylate placed over a corneal perforation can give the tissue time to heal, surgeons say.

Fairfield, Conn., surgeon Robert Noecker has used ReSure for both on- and off-label uses, and has gotten to know its idiosyncrasies. "This is a sealant, and is a derivative of the product DuraSeal, which is used by neuro-surgeons to seal the dura during cerebrospinal leaks," he says. "The key difference between a sealant and a glue is that the former is meant to go into a crevice and seal it, and it doesn't necessarily hold tissue together. Once the sealant is set in place, it takes on this rubber consistency and is very durable. It will stick around for at least a few days, and its advantage is it minimizes the use of sutures.

"I've used it for clear corneal wounds, and for instances in which I've removed a glaucoma tube shunt or there's a scleral defect and I wanted to seal the area," Dr. Noecker adds. "If you want to create a situation on the sclera where there's no flow or you want to seal up a hole you no longer need, it can be very useful. However, if the situation has a vigorous flow rate, it probably won't work that well. But, if you can get the area temporarily dry, it will seal scleral defects." Dr. Noecker says he'll often use it to seal wounds in cases where he's corrected astigmatism with a toric lens or incisions.

Dr. Noecker says working with ReSure has taught him some things. "The key is to be prepared to act quickly," he says. "You have about a five-second working time. This is important to note because when most people work with it, they're a little slow their first time. The sealant comes in a tray with a blue solution and a more particulate white component that you mix together. There will be a temptation to get all the white dissolved before you apply the sealant. The truth is, however, if you take all that time to get it dissolved, your window for working with it has closed. Be quick.

"Another thing I'd recommend doing is mix it under the operating microscope right next to the incision you want to seal," Dr. Noecker continues. "This way, when it's ready, the distance you have to move it is only a centimeter. Also, I'd tell surgeons to make sure the eye is dry. If there's an active leak or the surface is too wet, ReSure will tend to stick to itself rather than to the tissue you want to seal. The other thing is that it's best to get the application surface of the eye oriented in a horizontal plane, which may mean turning the patient's head a bit just so the sealant doesn't tend to flow away from where you're applying it. Since this will most likely be a temporal clear corneal incision you're sealing, you'll want the head oriented a little horizontally, or the patient looking a little toward his nose. It only takes a few seconds to set it in place, but you don't want it to run away from the incision."

Since ReSure costs somewhat more than a suture, Dr. Noecker says it's not something a surgeon will use in everyone. "It's more expensive than a suture, so you have to take that into account," he says. "As a skilled surgeon, will I use it on every case? No. But I will use it on premium cases such as femtosecond cataract. Fortunately, the risk of problems is low for cataract surgery, but there are cases in which I want to drive that chance of a problem down even lower by using the sealant in a particular patient." REVIEW

1. Agarwal A, Jacob S, Kumar DA, Narasimhan S. Handshake technique for glued intrascleral haptic fixation of a posterior chamber intraocular lens. J Cataract Refract Surg. 2013;39:3:317-22.

Donna McCune, CCS-P, COE, CPMA

A Delay for ICD-10– Now What?

A one-year delay in ICD-10 implementation brings up many questions for doctors and health-care organizations.

Q When did Congress announce the delay in ICD-10 implementation?

A On April 1, 2014, the Protecting Access to Medicare Act of 2014 (Pub. L. No. 113-93) was enacted, which said that the Secretary of Health and Human Services may not adopt ICD-10 prior to October 1, 2015. The delay was met with mixed reviews. The American Medical Association applauded the decision, citing the numerous regulatory burdens currently affecting physicians. The American Academy of Procedural Coders and the American Health Information Association encouraged physicians to stay the course and continue to prepare despite the delay.

Q Was there also a delay in implementing the new Centers for Medicare & Medicaid Services 1500 form that provides increased "space" for ICD-10 codes?

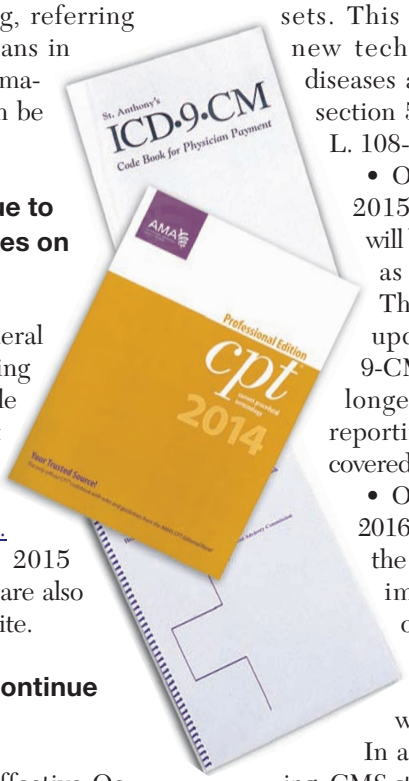
A No; version 02/12 of the CMS 1500 form replaced version 08/05 on January 1, 2014, with required use as of April 1, 2014. The new form contains additional space for reporting more diagnosis codes and increases the space for diagnosis codes of up to seven digits, which will be required for ICD-10. The new form also adds "qualifiers" for ordering, referring and supervising physicians in Box 17. Additional information on the new form can be found at nucc.org/.

Q Will CMS continue to update ICD-10 files on its website?

A Yes. The 2015 General Equivalence Mapping files are currently available on the CMS website at cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html. In addition, the 2015 ICD-9 and ICD-10 files are also posted on the CMS website.

Q Will new codes continue to be created?

A ICD updates are effective October 1 of each year. However, CMS recently published information on a code set "partial freeze" for ICD-10; it notes that ICD-9 will also be affected. The CMS posting states the following:



- On October 1, 2014 there will be only limited code updates to both the ICD-9-CM and ICD-10 code sets. This is to capture new technologies and diseases as required by section 503(a) of Pub. L. 108-173.
- On October 1, 2015, again there will be updates only as noted above. There will be no updates to ICD-9-CM, as it will no longer be used for reporting to HIPAA-covered entities.
- On October 1, 2016, one year after the new scheduled implementation of ICD-10, regular updates to ICD-10 will begin.

In a separate posting, CMS stated that there will be no new, deleted or revised ICD-10-CM codes for 2015.

Q Will CMS conduct additional front-end testing?

A Yes. CMS had planned a testing week in July 2014. This testing was cancelled due to the delayed implementation of ICD-10. CMS expects to conduct end-to-end testing in 2015; watch the CMS website and your local Medicare contractor websites for further details.

Q Was the March 2014 end-to-end testing successful?

A It was. CMS reports that testers submitted more than 127,000 claims with ICD-10 codes to the Medicare fee-for-service claims system and received electronic acknowledgement that their claims were accepted. Nationally, CMS showed an 89-percent acceptance rate for ICD-10 codes, which they considered a successful result. CMS also noted that some claims were purposely submitted with errors to test that errors would be identified.

Q Is it a worthwhile exercise to familiarize myself with the existing *ICD-10-CM Manual*?

A Definitely. There are many new concepts presented in ICD-10. The *ICD-10-CM Manual* contains four more chapters than ICD-9 and the number of code choices increases from 14,000 to 69,000. The guidelines published in the beginning of the manual are extremely instructive and provide a review of ICD-9 guidelines as well as introduce some subtle changes to coding with ICD-10.

Q Should I continue to train my staff during this delay?

A This is a great opportunity to better prepare them for ICD-10. Non-clinical staff will benefit with additional training on medical terminology and anatomy of the eye. The specificity of ICD-10 requires a higher-level understanding of ophthalmology for proper code selection.

Technicians and scribes can improve their documentation, especially with history taking. A fair amount of information required for proper ICD-10 code selection will come from the patient's history.

Q Is there any value in practicing our ability to select an ICD-10 code?

A Yes. By beginning to dual-code some encounters with ICD-10 codes, you will reveal vulnerabilities in your chart documentation that make code selection difficult or impossible. In addition, the more familiar you and your staff become with the manual, the less intimidating it will be in October 2015.

Q Are some ophthalmic diseases coded differently in ICD-10 than ICD-9, and will this necessitate a change in my current documentation?

A Yes, there are several. Glaucoma is a good example of a disease that is coded differently. Many physicians are lax with documenting the stage of glaucoma in a patient's medical record. Currently, few payers, if any, will deny a claim that does not contain the ICD-9 stage code. With ICD-10, your ability to select a code for glaucoma will require that the disease stage be documented.

For example, when coding appropriately for glaucoma with ICD-9 codes, the type of glaucoma is one ICD-9 code and the stage of glaucoma is a second ICD-9 code. A patient with primary open-angle glaucoma, moderate stage, is coded as 365.11 for the POAG and 365.72 to describe the moderate stage. In ICD-10, the stage is added to the ICD-10 code for POAG as a seventh digit. POAG, moderate stage in both eyes, is coded with one code in ICD-10, H40.11x2.

Physicians currently not documenting the stage of glaucoma should begin to stage the glaucoma now so that it is not a burden when ICD-10 coding begins.

Q What other documentation changes should we consider making?

A Because ICD-10 codes are more specific than ICD-9, there are many changes you can begin to implement.

1. Are your assessments as specific as possible? For example, if you note a corneal ulcer in your impression, are you indicating whether it is a central corneal ulcer, or a marginal ulcer or a perforated corneal ulcer?

2. Are your assessments specific to which eye or eyelid? For example, do you note in the impression if the patient has a chalazion on the left lower or left upper lid as opposed to just noting chalazion? Is the patient's nuclear sclerotic cataract in her right eye, left eye or both eyes?

3. For patients with a systemic disease and an ocular manifestation, are you indicating both the disease and the manifestation in the impression?

Improved documentation in the impression will facilitate more efficient selection of ICD-10 codes. It is not too soon to begin to make these changes in your current medical records.

Q Should we wait on ICD-10 and begin to prepare for ICD-11?

A No. ICD-11 only exists in draft form and is not expected until 2020 or 2025. REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.

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AMD=age-related macular degeneration; CAP=College of American Pathologists; CLIA=Clinical Laboratory Improvement Amendments.

The Critical Driver of Success: Physician Time

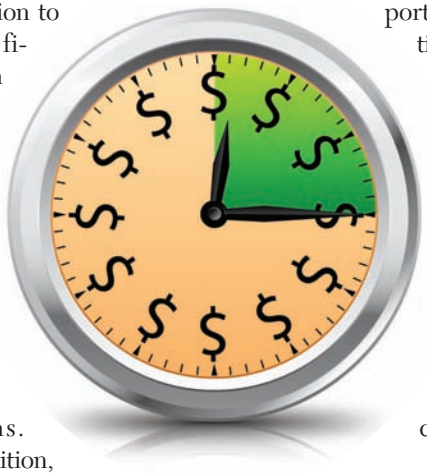
Charles P. Kroll, Chicago

Balance sheets and income statements are yesterday's tools, says this ophthalmic practice veteran.

Pop Quiz: What were you doing during the financial presentation at your last board meeting?

A. Texting your spouse
B. Checking e-mail
C. Stepping out to make a call
D. All of the above

Traditional financial reports of a balance sheet and income statement were conceived 150 years ago during the Industrial Revolution to facilitate railroad financing. Although their intent is to communicate the financial health of a business, the reports are spoken in the language of accounting, a language foreign to many physicians. Historical by definition, the statements are often presented weeks, if not months, after the fact.



Much like driving while looking in the rearview mirror, it's no wonder no one is paying attention.

To address this comprehension void and time lag, many medical practices rely on an assortment of ad hoc financial reports fueled by the PC revolution: key performance indicators; benchmarking; retrospective RVU analysis to make Henry Ford proud; and the most recent iteration, EHR dashboards designed by software engineers. Although providing number-centric feedback, this data tsunami drowns out the essence of your practice's financial success and most important asset: physician time.

In this article, I'll lay out three steps that wed the concept of physician time with financial management, promoting physician understanding and ownership of financial performance.

Step 1: Doctor Days

Build the foundation of your practice's financial management, budgets and projections on physician and optometrist time, or "doctor days," rather than relying on accounting department edicts or RVU-based budgets. Simply put, calendar out doctor days (or half days) by type of service: clinic; ASC;

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and hospital. This process links, in an easy to understand manner, financial performance with the investment of physician time, while de-emphasizing esoteric accounting reports.

Applying estimated gross charges and net revenue by doctor day by type of service closes the loop, producing accurate and predictive budgets in the aggregate, and by individual physician and OD type of service and location. One payoff is the ability to evaluate the ratio of doctor time to various financial and patient-care metrics. For example, 19 percent of total doctor clinic time is invested at a particular location providing 11 percent of patient visits.

Implementation of the doctor day model transforms your sclerotic annual budget—typically approved and forgotten hours before the annual holiday party—into a living document capable of capturing the financial impact of changes in budgeted doctor days, e.g., new physician or OD hire. Married to actual year-to-date numbers, "flex" your budget based on anticipated doctor days, and avoid the 8th Deadly Sin: negative physician compensation and taxable income news after year-end.

Divorced from procedure volume and RVU-driven mock-ups, the doctor day model is an effective tool to evaluate and negotiate value-based contract proposals from payers. Historical fee-for-service data, converted to doctor days, can be developed to determine an acceptable return on the investment of physician time for anticipated covered lives and patient encounters, the cornerstone of any successful risk-sharing contract negotiations. Level the playing field against health plan actuaries, and negotiate with confidence.

Finally, aside from patient-care and outcomes considerations, make informed decisions to opt in or out of government incentive programs based on incremental doctor days required to offset penalties in the event you opt out. For example, from a time perspective, 1 percent of 200 doctor days per year is two days, or about 1.3 hours per month (20 minutes per week, 4 minutes per day) assuming 100 percent government payer mix.

Step 2: Real-Time Reports

While the argument has been made that profit margins on many surgical procedures render real-time financial reporting unnecessary for medical practices, common sense and the current health-care reimbursement environment suggest otherwise. Lack of timely, actionable information masks and enables a multitude of sins: payer and contracting issues; clinic workflow and appointment scheduling; front desk proficiency and business office effectiveness; and yes, unscheduled physician time off.

Focus on these three words and follow their corresponding rules: simple; time; and visual.

- Rule #1. Simple. Keep reports simple and relevant: production; cash collections; a few key patient-care barometers, e.g., visits, cataracts and refractive
- Rule #2. Time. Present data in terms of time, e.g., cash collections are 1.2 days behind month-to-date budget
- Rule #3. Visual. Present information visually with intuitive charts, rather than raw numbers or text explanations.

Step 3: On-Line Access

Establish a secure one page Intranet for one-click access to real-time and historical financial reports from a smartphone, tablet or laptop. Notification of time-sensitive updates can be pushed out via e-mail or private Twitter feed. Granted, while most physicians prefer to "just practice medicine," this step democratizes the financial reporting process and fosters a culture of transparency and accountability.

Both the Intranet and real-time report templates can be updated and maintained by current staff utilizing Word, Excel and existing practice management software, bypassing cumbersome Sharepoint altogether. Finally, the best kept secret in the EHR industry: pre-loaded and license-free Internet browser reporting tools are available for EHRs running on Microsoft's SQL server platform.

Although these simple steps won't render traditional financial reports obsolete, taking mind-numbing numbers, meaningless minutiae and disjointed data off the table removes the psychological barriers to financial comprehension, encouraging healthy physician and management dialogue regarding both short-term clinic operation objectives and long-term strategic financial planning.

You can now relax guilt-free and text your spouse, check e-mail and make calls during the HR director's presentation!

Stop driving by the rearview mirror using Industrial Age financial management and reporting tools, and embrace the Information Age. You already know where you've been. Keep your eyes on the road, your hands upon the wheel: Know where you are today (Steps 2 and 3) and where you're going (Step 1).

Focus on your most important asset—physician time—and strengthen and grow your practice's financial health by responding to changing circumstances in the here and now, built on the foundation and communicated in the language of time. REVIEW

Mr. Kroll has 20 years of healthcare experience, including 11 years with Minnesota Eye Consultants, P.A., providing financial management and consulting CFO services to independent and hospital-affiliated specialty and primary-care medical clinics. Contact him at cpkroll@gmail.com or on Twitter at https://twitter.com/CharlesPKroll.

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The Devil's in The Distant Details

Walter Bethke, Managing Editor

Wide-field angiography systems can help catch peripheral ischemic areas that portend worsening disease.

There's an old saying that goes, "What gets measured, gets done." In the world of retinal care, it could be paraphrased as, "What gets seen, gets treated," since a retinal specialist can't address issues he can't see, and might even categorize a patient's disease differently if he saw retinal features that didn't appear on conventional angiography. This is especially true in cases of diabetic retinopathy and retinal vein occlusion, where peripheral retinal features might have an impact on the patient's condition. Here, experts explain why they've found value in examining the far periphery with very wide-field retinal systems, and offer tips for getting the best images.

The Systems

For angiography of the typical diabetic retinopathy or vein occlusion patient, there are three main systems that clinicians routinely use.

• ***Heidelberg wide-field viewing module.*** This is an add-on, non-contact lens for the Heidelberg Retinal Angiograph-2 or the Spectralis OCT that allows the user to select an angle of view of 51 degrees, 68 degrees or 102 degrees when doing fluorescein angiography. Users say that, with some "steering" of the patient to get him to look in certain directions as the test proceeds, the system can add to the field of view. "Its wide-field setting is 102 degrees," says Jarrod Wehmeier, ophthalmic photographer at the Retina Institute in St. Louis. "However, I think you can add 20 to 30 degrees in each direction by having the patient look around in different directions."

The Retina Institute's Gaurav Shah, MD, who consults for Heidelberg, says one advantage to him was that the wide-field viewing was just an add-on for an instrument he already owned, rather than a new capital equipment purchase in the six-figure realm. "It didn't make sense to spend the extra money vs. just getting an add-on lens that costs about $20,000," he says.

Some users say that just hitting the "acquire" button on the HRA2 or Spectralis with the wide-screen module might not produce the best resolution images in some cases, and that's why the machine offers an image averaging feature called automatic real time image stabilization, or ART. "I'd suggest using the ART button with single frames to greatly increase your resolution," says Mr. Wehmeier. "This locks onto the retina and takes 10 frames and overlaps them to increase the resolution of the image."

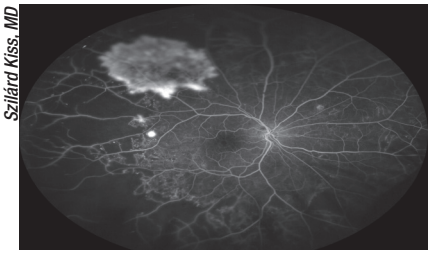
• ***Optos 200Tx.*** The non-contact Optomap 200Tx allows clinicians to

acquire angiographic data on the retina with a 200-degree field of view. As with the Heidelberg wide-angle viewing system, the user can steer the Optomap patient, yielding an even larger area for examination. "Sometimes people forget you can steer the patient with the Optos," says Szilárd Kiss, MD, director of clinical research and associate professor of ophthalmology at Weill Cornell Medical College in New York City. "If the photographer sees something he wants to focus on, he can still steer the patient's gaze."

When a user views Optomap images, Dr. Kiss says there are some aspects he'll need to get used to. "There are some trade-offs that are inherent in all wide-field imaging systems as well as the ellipsoid mirror used by Optos," he says. "When one views a spherical surface on a flat monitor, the periphery will not have the same representation as the posterior pole. This is akin to the same issues faced by mapmakers in which their maps make Greenland appear several times the size of the U.S., when in fact, it is about one third the size." Dr. Kiss points out that there are software fixes that are now being worked on to correct for this peripheral non-linearity.

"Some have talked about the Optos losing some resolution in the posterior pole," Dr. Kiss adds. "But this is unfounded. I always challenge my colleagues to show me something on conventional imaging in the posterior pole that you couldn't see on wide-field imaging. You can see everything in the posterior pole that you need to see with the Optos ultra wide-field image."

• ***Staurenghi lens.*** This is a contact-lens based viewing system that attaches to a scanning laser ophthalmoscope such as the HRA2. It can provide a 150-degree viewing field, with the drawback that it needs to make direct contact with the patient's cornea in order to make this view possible. Though it yields good images, Dr. Shah says a non-contact system often suits the patient flow of his practice better. "We find it difficult to use a contact system with the volume of patients we see," he explains. "Even though it may give better images, sometimes you have to make sure you can do a test efficiently."


Szilárd Kiss, MD

In this patient, the posterior pole looked essentially normal, but an Optos ultra wide-field view showed extensive disease.

It's worth noting that though the contact RetCam system does wide-field imaging, it's almost exclusively used for diagnosing and managing retinopathy of prematurity.

Putting the Systems to Use

Users of wide-field systems say that, when you use them properly, they may provide information that you might have otherwise missed. Here are the potential benefits of wide-field imaging, and tips on how to achieve them.

• ***Extra information.*** Before wide-field imaging systems, clinicians relied on the seven standard fields, which involved the use of traditional lenses aimed at different areas of the retina to form a composite image that provided approximately a 75-degree field of view. "The seven standard fields used to be the gold standard in viewing conditions such as diabetes," remarks Dr. Kiss, who adds that retina specialists have always been interested in seeing more of the retina, but were just limited. "Now, examining the periphery as Lloyd Paul Aiello, MD, and our group have done in some of our studies has made us realize that the classification of a patient's disease can actually change based on peripheral features," Dr. Kiss says. "Dr. Aiello found that patients' disease severity may be different depending on where the lesions are located,[1] and he found that a third of the lesions were outside the standard viewing fields. If you've got more lesions in the periphery, a patient may progress faster. Knowing details such as these will influence how often you follow-up with a patient and perhaps even when he's going to need treatment based on the condition of his peripheral retina."

Dr. Shah says that he also appreciates the extra information he acquires, even if the exact relevance to treatment is still a matter of debate. "It gives us the views we need of the periphery to look for areas of ischemia, especially in cases of retinal vascular disease such as vein occlusions and diabetic retinopathy," he says. "There are still conflicting reports regarding whether or not treating ischemic retina makes a difference in persistent macular edema. However, I think that in patients who have ischemia the VEGF load is greater than in non-ischemic eyes, so detecting it may give us an opportunity to supplement or augment our other therapies such as anti-VEGF and steroid injections or laser. It also gives you a way to identify people who will probably keep experiencing disease recurrences. In addition, we know that ischemic eyes have a worse prognosis. Ultimately, I think having information on ischemic areas in the periphery allows a physician to tailor his therapy to the patient or modify existing therapy, as well as providing a way to monitor the patient during follow-up."

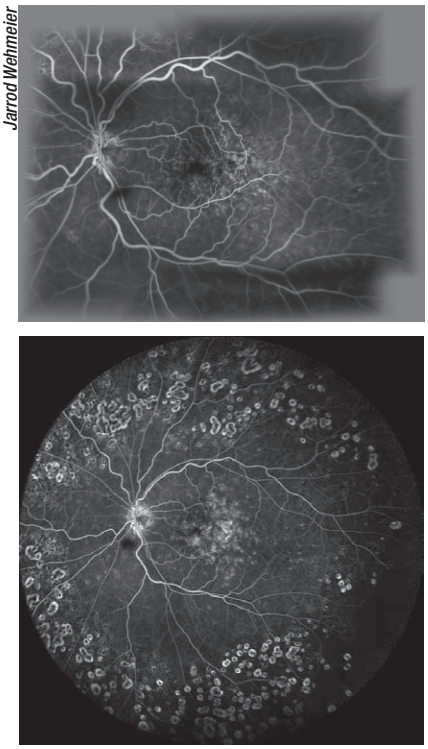
The nature of angiography itself may make wide-field imaging's information more useful than just creating a montage of single images from a traditional lens. "If you're using a traditional-sized lens to shoot five or six photos around the globe to get the peripheral retina, you may be off by one or two minutes compared to the dye circulating in the eye," notes Dr. Kiss. "By the time the patient resets and then you reset, you

may not get the pathology. Also, with a montage it helps to know what you're looking for. If you've got a patient with a pathology in the superotemporal quadrant of the far periphery, it's easy to tell the photographer to focus on that. But if you have a patient in whom you're not sure where the pathology is, the wide-field imaging will get it all."

Dr. Kiss says there's preliminary data from single-site studies that laser treatment based on peripheral retinal data might reduce the treatment burden in the future. "First, a caveat: This all remains to be proven in larger, multicenter trials, but there's some indication that, in patients who have an incomplete response to anti-VEGF therapy—as well as the so-called 'VEGF-addicts'—you could perhaps laser the peripheral ischemia and reduce the amount of anti-VEGF treatment you need.

"In vein occlusion," Dr. Kiss continues, "if you look at the posterior pole, you'll see a small vein occlusion. "But when you look in the periphery with ultra wide-field imaging, you get a sense of the extent of the disease and the disease burden. That might be why a patient needs a lot of anti-VEGF injections or multiple Ozurdex treatments. So, instead of lasering the macula, one could imagine an approach where you laser the periphery and maybe decrease the ischemic drive that way. The same thing might also be true in diabetes. We and others have published that the areas of non-perfusion in the periphery are correlated with the presence or absence of diabetic macular edema.[2] Though that doesn't imply causality, once again one cannot only imagine using this to quantify the disease burden but perhaps also treating those peripheral areas to help preserve the posterior pole and maintain a patient's vision rather than lasering the posterior pole and possibly compromising vision."

• ***Tips and techniques.*** Mr. Wehmeier says that, when working with the Heidelberg's wide-angle viewing system, it can help to make some adjustments before the angiography study begins. "When you bring the patient into the chinrest, since the size of the lens is quite large you have to have the patient turn his head to a 45-degree angle," he explains. "This isn't a tilt of the head, just a turn. This is so the lens doesn't hit his nose and he can look straight ahead. It gives you a nice viewing area. Also, if possible, have another person hold the lids open to make the imaging easier for you and avoid lash artifacts. I've been able to do it usually with a Q-Tip and have gotten great images but, if you really want to document something in the periphery, it can be helpful to have someone else on-hand. This is especially true for the first couple of times you're doing it just to get used to the machine's operation." Mr. Wehmeier says he injects the fluorescein as quickly as possible, and uses the entire 5-cc injection. "I usually try to use 5 cc in five seconds," he explains. "You're going to need as much dye as possible in as short a time as possible in order to get a high-contrast image. If you only inject 3 cc, you'll notice there's not enough dye to fill the images and you'll lose quality."



Jarrod Wehmeier

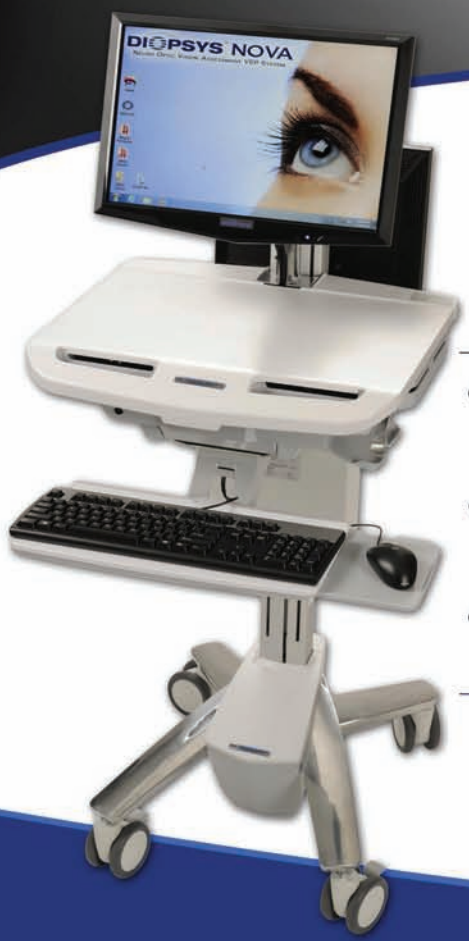
Experts say that using a montage composed of several individual images (top) may not be as effective as one wide-field image (bottom, same patient).

In addition to using the ART feature described earlier to average the Heidelberg's images, Mr. Wehmeier also says adjusting the device's gain, or the overall brightness of the image, can help. "I try to adjust the gain so it's up as high as possible first," he says. "This will make for a grainy image at first but, once the dye hits the eye—when you start to see choroidal flush—I turn the gain all the way down and let the dye fill in and do its work."

Dr. Kiss says that, with the Optomap, there's a learning curve in dealing with the patient's lids and lashes. "The patient is pressed up against the device, so you have to make sure the lids are out of the way," he says. "You have to make sure he's in the best position to get an optimal image in the superior and inferior quadrants. Some colleagues use a Q-Tip to get the lids out of the way, but we've found the photographer's finger works just as well. Occasionally, the patient can hold up his upper lid to get rid of that lash artifact."

Dr. Kiss says getting peripheral retinal details is a relatively recent development but not a new concept. "The idea that the peripheral retina is important isn't something new," Dr. Kiss says. "Looking back at the original discussions of diabetic retinopathy by the giants in retina, they acknowledged the importance of the periphery, but couldn't image it efficiently. Now we can." REVIEW

1. Silva PS1, Cavallerano JD, Sun JK, Soliman AZ, Aiello LM, Aiello LP. Peripheral lesions identified by mydriatic ultrawide field imaging: Distribution and potential impact on diabetic retinopathy severity. Ophthalmology 2013;120:12:2587-95.
2. Wessel MM1, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. Br J Ophthalmol 2012;96:5.



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Maximizing the Benefits of Anti-VEGF

Christopher Kent, Senior Editor

Expertsdis cuss how the options compare, how they can most effectively be used and what's in the pipeline.

The advent of anti-VEGF drugs has caused a revolution in the treatment of diseases such as wet age-related macular degeneration and diabetic retinopathy. Today, the field continues to move forward as researchers and manufacturers work to improve the outcomes produced by drugs such as Avastin (bevacizumab), Lucentis (ranibizumab) and Eylea (aflibercept), and try to find ways to reduce the number of intraocular injections required for effective treatment.

Here, three experts in the field discuss the current developments in this area, and offer their thoughts about what may lie ahead.

Avastin vs. Lucentis

The difference in price between Avastin and Lucentis has been a pivotal factor in the popularity of Avastin, but differences in effectiveness and safety are still being debated. "Both Avastin and Lucentis are potent, highly effective molecules—at least for wet macular degeneration—and they've been shown to produce similar visual outcomes," says K. Bailey Freund, MD, a retina specialist who practices at Vitreous-Retina-Macula Consultants of New York and is a clinical professor of ophthalmology at the New York University School of Medicine. "A number of studies have compared the drugs head-to-head. It appears that Lucentis does a little bit better job of getting the macula dry and keeping it that way. In the CATT study, for example, more eyes had fluid with Avastin than with Lucentis, and patients who were treated only when they had fluid required fewer injections with Lucentis than Avastin."

Dr. Freund notes that the differences between Avastin and Lucentis are more obvious when addressing conditions other than macular degeneration. "In wet macular degeneration there's not a whole lot of VEGF being expressed that needs to be inhibited," he points out. "In contrast, in acute central retinal vein occlusion there are extremely high levels of VEGF expression, so we tend to see more of the differences between the drugs when treating this condition. That's also true in some patients with diabetic retinopathy. In my experience, the commercial drugs work better than Avastin in these situations, so I prefer to use them."

Peter K. Kaiser, MD, the Chaney Family Endowed Chair in Ophthalmology Research at the Cleveland Clinic Lerner College of Medicine, and professor of ophthalmology at the Cole Eye Institute, agrees that vein occlusions may call for a different

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Comparison of Clinical Trial Results and Costs of Anti-VEGF Drugs

	Ranibizumab 0.5 mg	Bevacizumab 1.25 mg	Aflibercept 2 mg*
Main randomized clinical trials	ANCHOR (n=423) MARINA (n=716) CATT (n=1,185) VIEW (n=2,457)	CATT (n=1,185)	VIEW 1 (n=1,217) VIEW 2 (n=1,240)
Patients avoiding a loss of 15 letters at two years	ANCHOR: 89% (monthly arm) CATT: 92.8% (PRN arm); 93.3% (monthly arm) VIEW: 92% (monthly arm)	CATT: 88.4% (PRN arm); 92.2% (monthly arm)	VIEW: 92% (monthly arm); 92% (q8 arm)
Patients who gained 15 letters at two years	ANCHOR: 41% (monthly arm) CATT: 30.7% (PRN arm); 32.8% (monthly arm) VIEW: 32% (monthly arm)	CATT: 28.3% (PRN arm); 31.8% (monthly arm)	VIEW: 31% (monthly arm); 33% (q8 arm)
Mean change in visual acuity at two years (letters)	ANCHOR: +10.7 (monthly arm) CATT: +6.7 (PRN arm); +8.8 (monthly arm) VIEW: +7.9 (monthly arm)	CATT: +5 (PRN arm); +7.8 (monthly arm)	VIEW: +7.6 (monthly arm); +7.6 (q8 arm)
Mean number of treatments at two years	ANCHOR: 21.3 (monthly arm) CATT: 12.6 (PRN arm); 22.4 (monthly arm) VIEW: 16.5 (monthly arm)	CATT: 14.1 (PRN arm); 23.4 (monthly arm)	VIEW: 16 (monthly arm); 11.2 (q8 arm)
USFDA approval	June 2006	Off-label use	November 2011
Approximate cost of drug	$1,991.55	$23.48	$1,961
Reimbursement per injection**	$118	$118	$118

PRN=as needed. q8=every eight weeks. All drugs given as intravitreal injections with three initial monthly injections. Table based on Freund KB, et al., 2013.[3]
* VIEW data integrated from VEW 1 and VIEW 2.
**Reimbursement by Medicare part B in 2013 in New York State.

approach. "Macular degeneration is not really a VEGF-driven problem, whereas retinal vein occlusion and diabetic macular edema are," he says. "Because of that, clinically we are seeing a bigger difference in efficacy between drugs, although we don't have a comparison study yet to demonstrate that one drug is superior to the others. We will have results from a study comparing Lucentis, Avastin and Eylea for treating diabetic macular edema later this year. But for CRVO, we currently have no guidance until the SCORE 2 study is finished.

"I think with all of these diseases, many of us start with Avastin and only switch to a different drug when the patient doesn't do as well as we expect. There's really no reason to start with the more expensive drug."

Dr. Freund notes that the obvious issues with Avastin are potential concerns of safety; in particular, the issue of compounding pharmacies. "In rare situations the drug has become contaminated, and in other countries such as China there have been issues with counterfeit Avastin being compounded," he says. "But beyond those kinds of concerns, the CATT trial did show that there was a small, statistically significant difference between Avastin and Lucentis in terms of systemic safety, although it wasn't one particular systemic adverse effect; it was distributed over many things. The difference was in favor of Lucentis, but it was a small difference, and many people have discounted it because it didn't make a whole lot of sense. The systemic safety problems weren't necessarily linked to the mechanism of action of the drug. Also, the other studies didn't find that difference."

Dr. Kaiser feels the evidence of safety differences doesn't warrant a change in protocol. "From a standpoint of safety—outside of the compounding issue, which is still a big concern—there's no compelling evidence that Avastin has any additional safety issues," he says. "For most of us, that gives us the green light to use Avastin more frequently. Certainly many practices have turned to using Avastin first in all patients. They only switch the patient to another drug if Avastin fails to produce the desired result."

"Overall, the Avastin vs. Lucentis debate has become a hotly contested area," adds Dr. Freund. "Some people firmly believe that Avastin is as good as the other options in every way, at least for treating macular degeneration, while others point out the somewhat small but potentially real differences."

A Third Option

With the Food and Drug Administration approval of Eylea in November 2011, surgeons had two approved anti-VEGF drugs to choose from, in addition to the off-label use of Avastin. This further enlivened the debate regarding which—if any—is superior.

Dr. Kaiser notes that the VIEW study in macular degeneration found Eylea to be similar in efficacy to Lucentis, while requiring fewer injections. "In this study, patients were able to go longer between treatments with Eylea than Lucentis," he says. "Whether that difference remains in clinical practice remains to be seen. We are finding that many of our pa-

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tients who fail to respond to Avastin or Lucentis do better when we switch them to Eylea, and several case series have found the same thing. So in my practice, I often start patients with Avastin. If they don't respond to Avastin, I switch them to Eylea because of the longer duration, similar efficacy and lower cost compared to Lucentis. The exception would be diabetic macular edema, for which Eylea is not approved. In that situation I'll switch to Lucentis if Avastin fails."

"Eylea is very effective," agrees Dr. Freund. "Our group and others have shown that some patients do seem to respond somewhat better anatomically—in particular, those who have proven resistant to the alternatives. Switching them may allow for less-frequent dosing. It's labeled for eight-week dosing after the first three monthly treatments, which is quite different from the Lucentis label."

David M. Brown, MD, FACS, who practices at Retina Consultants of Houston and runs the Greater Houston Retina Research Center, has written extensively about the use of the different anti-VEGF options in macular degeneration, diabetes and retinal vein occlusion, and their comparative efficacy. "In terms of durability—getting the retina dry and keeping it that way longer—I think Lucentis and Eylea are definitely better for treating diabetic macular edema, and I think those drugs are better for at least half of all macular degeneration patients. If you look at the data from the CATT trial, monthly Avastin dried out about 30 percent of patients, while monthly Lucentis dried out about 50 percent. In Regeneron's VIEW 1 and VIEW 2 trials, Lucentis dried out about 50 percent of eyes, similar to the CATT results, and Eylea dried out about 70 percent. That suggests that you'll get more effective drying with Eylea than with Lucentis or Avastin.

"I believe that most people who have worked with all of these drugs extensively know that Avastin is less potent than the others," he adds. "Even in the CATT trial, Avastin didn't win in any category. Usually if you have drugs that really are equal, one drug will win in one category and the other will win in another category. Avastin didn't win in any category. People keep saying that Lucentis and Avastin are equal, but if it's my eye or my dad's eye that's in trouble, I'm using Lucentis or Eylea if I have a choice. However, as I said earlier, if you succeed in drying the retina out, it doesn't matter which drug you used. So, I think it's very reasonable to start with the cheaper drug.

"The biggest thing happening with Eylea is that they have a pending investigational new drug approval for diabetes," he adds. "That could really change diabetes management, depending on the outcome of the direct head-to-head comparison of Lucentis, Avastin and Eylea for diabetes that's in progress right now. The data should be out in January. My guess is that Eylea will turn out to be more durable, but we won't know until we see the data. If it shows that Avastin is absolutely equal in every way, then I think every insurer will say you need to use Avastin, and that's fine. If it shows that Eylea or Lucentis (or both) are superior, then we'll be in the same situation we are with macular degeneration."

Dr. Freund points out that Eylea was tested in two strengths: 0.5 mg and 2 mg. "It's the 2-mg formulation

Scheduling Intravitreal Injections

One key issue with the intravitreal injection of anti-VEGF drugs is finding ways to avoid giving more injections than are truly necessary. "For the most part I use a treat-and-extend treatment regimen," says Peter K. Kaiser, MD, the Chaney Family Endowed Chair in Ophthalmology Research at the Cleveland Clinic Lerner College of Medicine. "I try to treat until the patient is dry and then extend the time interval between the injections. We now have good evidence from the LUCAS study showing that this works very well. As-needed scheduling has been shown to be less efficacious than monthly treatment, but by only a few letters. So I think it's perfectly fine to not use fixed dosing. Of course, it's not wrong to use fixed dosing—in fact, it's the gold standard—but it's too much of a burden on the patient to come in every month for treatments."

K. Bailey Freund, MD, a retina specialist and clinical professor of ophthalmology at the New York University School of Medicine, is the originator of the treat-and-extend protocol. "Treat-and-extend has become the most widely used treatment regimen, despite the fact that there's minimal randomized clinical trial evidence showing that it works as well as monthly dosing or the Eylea regimen or OCT-guided therapy," he says. "Only one prospective, randomized trial, the LUCAS trial, showed impressive results for the treat-and-extend regimen. But despite the limited data, retina specialists have gravitated towards it; if you look at the annual survey of the American Society of Retina Specialists, the preferred treatment regimen has gradually moved toward treat-and-extend."

"Some surgeons still do p.r.n. scheduling," notes David M. Brown, MD, FACS, who practices at Retina Consultants of Houston and runs the Greater Houston Retina Research Center. "I think that's wrong because I don't think it's ever a good thing to have recurring edema. Some physicians do the injections monthly, but I'd say the majority of higher-volume surgeons—probably 90 percent—use treat-and-extend."

"Patients differ widely in terms of how often they need injections," Dr. Freund adds. "When you do treat-and-extend you're individualizing the treatment, finding those patients who need more injections and those who need fewer, so patients come in when they actually need the injection, not just every month rigidly."

—CK

that was approved, so we're giving a fairly large dose of drug," he notes. "Whether the drug itself is truly more potent than the others or we're just giving more of an equally potent drug is still debated. But I think most retinal specialists have the impression that Eylea is somewhat more potent.

"Increased potency sounds really good," he continues, "but there's a concern that comes from the CATT and IVAN studies, the latter being the U.K. head-to-head comparison of Lucentis and Avastin. In both studies it was seen that patients who got more injections developed more geographic atrophy. That's a big problem, because that's often how patients end up losing vision over the long term; retinal cells die. So, a drug that's more potent might reduce the number of injections needed but cause more geographic atrophy. It's a theoretical concern at this point, but some people like myself are watching this very carefully. In our zeal to get maculas completely dry we could potentially be accelerating the dry aspect of the disease.

"If this is true," he adds, "it will be hard to prove. It's possible that if we analyze some of the data from recent trials we may be able to tell whether higher doses cause more geographic atrophy. But geographic atrophy is part of the natural course of the disease, so it will be hard to tease apart what the drug might be doing vs. the disease itself."

Dr. Brown says he uses whichever drug keeps the retina dry. "If Avastin keeps the retina dry, whether it's macular degeneration or retinal vein occlusion or diabetes, that's fine," he notes. "If however, you're giving a patient a shot of Avastin every month and he still has persistent fluid, I think the patient would be better served by trying Lucentis or Eylea."

The Insurance Factor

"The drug a surgeon uses depends in part on the insurers," notes Dr. Brown. "More and more insurers are either doing a step edit, where they want you to use Avastin first, or they're simply using a passive-aggressive strategy to avoid dealing with surgeons who use the expensive drugs. Medicare advantage plans are not supposed to restrict drugs any more than Medicare—they're supposed to provide the same thing Medicare does. So they say you can use any drug you want, and then they drop providers who use the more expensive drugs. They say they're making their provider pool smaller or consolidating, but if you look at the pool, the only people they keep on are doctors who never use Lucentis or Eylea. I've been kicked off of, or not selected for, most Medicare Advantage plans and HMOs in our market because I use Lucentis and Eylea in recalcitrant patients.

"Of course, this would never happen except in such an unusual situation," he adds. "There's no place else in medicine where you have a $50 drug competing with a $1,300 or $2,000 drug. And we're in such a small field that they can kick us off their panels and it saves them money."

Dr. Brown points out that many insurers won't even allow a step edit. "I wish the insurance companies would allow that, even though the Centers for Medicare & Medicaid Services has said that step edits aren't appropriate," he says. "As a result, in our practice we have to take the patient's insurance into consideration. We know which insurers want us to use Avastin, even though they don't say it. Patients with that insurance only get Avastin. With other patients we can do what we think is the best for the patient."

Although Dr. Brown believes it's reasonable to start a macular degeneration patient on Avastin, he notes that occasionally a patient won't agree. "Patients," he says, "sometimes make this argument: 'I've got great insurance and I've been paying for it for

a long time. Why are you making me start with a drug that's not made to go into the eye and has a risk of endophthalmitis from a compounding pharmacy issue?' In the final analysis, if a patient has good insurance, I start him on an approved drug—Lucentis or Eylea. If the patient is cash-pay or underinsured, I start him on Avastin. If that patient has lots of fluid, then I fight the insurance company to try to get one of the other drugs.

"Another option is to get the patient into one of the Access programs," he notes. "The Access programs are pretty good at getting free drugs for patients who can't afford them. These are charities originally developed by the pharmaceutical companies to provide access to chemotherapy for cancer. If you make less than $100,000, you can get free Lucentis or Eylea—but only if you don't have insurance coverage. So the irony is that if you have a Medicare advantage plan that says 'Yes, we cover Lucentis,' you're not eligible for the free drug. At the same time, you're not really eligible for the insurance-covered drug, because your surgeon may be fired from the insurer's panel if he uses it."

Combination Treatments

For a number of reasons, one popular approach to trying to improve on the current drugs has been to look for new drugs and other procedures that might combine with the current drugs and produce even better outcomes. "Studies have looked at combining anti-VEGF drugs with photodynamic therapy, steroids and radiation," notes Dr. Freund. "The problem is that these combinations sometimes reduce the number of injections needed, but none of the combination trials has yet matched the visual results achieved with anti-VEGF monotherapy.

"The exception may be combining anti-VEGF with another sophisticated pharmacological agent," he continues. "There's a drug called Fovista, currently undergoing a Phase III trial in combination with Lucentis; the combination is being evaluated in comparison with Lucentis monotherapy. Fovista targets platelet-derived growth factor, which is involved in the development of the pericytes that help in the maturation of neovascular vessels. In other words, Fovista inhibits the pericytes."

Dr. Kaiser believes that in terms of combining drugs, using a PDGF inhibitor is at the top of the list. "Fovista is the first out of the gate," he says. "The Phase II study showed very good results in comparison to anti-

VEGF alone, resulting in a significant improvement in vision. If that's replicated in Phase III, they'll have a hit on their hands because we'll have a treatment that actually improves vision over our current anti-VEGF therapies. Of course, this means patients would undergo two injections, but they won't care as long as they're getting better results. My patients would be willing to do three or more injections every month if it would improve their vision, especially since they would be done at the same visit."

"Regeneron and Bayer have also announced that they're working on an anti-PDGF agent," Dr. Freund notes. "The potential benefit of their formulation is that it could be co-formulated with Eylea. In contrast, in the Fovista trial the patients have to get two injections back-to-back; you can't mix the two drugs. So if the strategy of using Fovista in combination with one of the existing drugs gets FDA approval, it will have to be given the same way. That's a drawback, so the trial will need to show a fairly substantial benefit over Lucentis alone to make it something that doctors and patients would want to do. But it's certainly possible. Also, if you did this a number of times it might result in fewer injections being needed down the road, but we don't know if that will be the case."

Dr. Freund says another potential combination drug worth noting is squalamine lactate, a topical therapy. "That's being used in combination with anti-VEGF in hopes of reducing the treatment burden," he explains. "It's currently in clinical trial. It's felt to be a fairly potent antiangiogenic molecule that can reach therapeutic levels in the retina with topical dosing."

Dr. Brown notes that there are some Phase I trials combining other antiangiogenic agents with an anti-VEGF drug. "One that's combined with Lucentis is coming from Roche; another that combines with Eylea is from Regeneron," he says. "It's nearly impossible for anyone other than a big pharmaceutical company to conduct a trial like this, because only they can provide the anti-VEGF drug without having to buy it. In any case, these options are three to seven years away, assuming they pan out. In the near future, however, there is a proposed Phase III trial of an Alcon anti-VEGF drug that looks encouraging."

Dr. Freund adds that the reason many of these are combination trials is that it would be unethical to do a trial of a drug vs. placebo. "This way the subjects in both groups get a proven therapy, and maybe the group getting the new drug won't need as many injections," he explains. "In the case of squalamine lactate, I also believe it would be a bit of a reach to think that any drug used topically as monotherapy could compete with a drug being injected intravitreally."

Anti-VEGF and Radiation?

In terms of combining anti-VEGF with radiation, Dr. Freund says studies have not borne out the Neovista approach. "The Neovista approach involved doing a vitrectomy and inserting a probe into the eye," he says. "Now there's an office-based IRay radiation system that uses external beam radiation that's in clinical trials. But I am skeptical that radiation is really going to be an effective treatment. It has a fairly narrow therapeutic window. If you give too much you'll cause radiation retinopathy; if you give too little, it may not impact the disease you're trying to treat."

"Radiation in combination with anti-VEGF therapy is still being looked at," notes Dr. Kaiser. "It's gotten farther in Europe than in the United States. The INTREPID study for Oraya's IRay system has shown a decrease in the number of injections, with similar visual results, when used in combination with anti-VEGF. It's only approved in Europe, but we're hoping for a Phase

III study in the United States."

Dr. Brown believes combining anti-VEGF drugs with radiation is unlikely to be widely adopted. "The data shows that doing this doesn't produce improved visual acuity," he points out. "I present at meetings every month and talk about anti-VEGF trials where patients gained two or three lines, so an alternative that doesn't lead to improved vision, to me, is not viable."

Staying Out of Trouble

These strategies can help prevent problems from arising:

• ***When treating diabetic macular edema, don't wait to start the injections.*** "The data shows that if you wait a year, you never get the gains you would have gotten," Dr. Brown points out. "No matter which drug you're using, start injecting these patients sooner rather than later. Nobody holds off injecting patients with macular degeneration, because everybody knows that the eye will be far worse off in a couple of months if you don't treat. With diabetes, it's a lot easier to postpone starting while you're managing other things such as blood pressure control and systemic concerns. But the longer you wait to start injections, the less chance you have of robust gains."

• ***Be especially careful about managing your cash flow relating to Lucentis and Eylea.*** "More and more we're seeing some secondary insurers dragging their feet about paying their portion of the coverage," says Dr. Brown. "If you're using anything other than Avastin and 10 percent of your secondaries are delaying payments for a while, stretching them out to 90 days or more, you might not notice it at first because some money is coming in. But the delay in reimbursement can add up and really hurt your practice. You need to figure out which insurers are delaying payments, and then either talk to those insurers or consider using mostly Avastin with patients who have that insurance.

"Sequestration has also made it harder to use Lucentis and Eylea by cutting the margin from 6 percent to 4 percent," he adds. "That makes it even tougher to manage these drugs."

• ***Pay attention to your compounding pharmacy.*** Dr. Freund notes that managing compounding pharmacy concerns is tough. "You attempt to evaluate your pharmacy as much as possible, but you can't know for sure what procedures are being followed in actuality," he says. "I've had the unfortunate experience that three of the compounding pharmacies I've used over the course of my career—all except the one I'm currently using—were shut down by the FDA because of serious concerns. Years ago I ordered some drug from the New England Compounding Pharmacy; that was the one that had the fungal contamination of steroids that killed patients with encephalitis. Franks Pharmacy, in Pensacola Fla., was shut down for fungal contamination of drugs. And the pharmacy that I was using up until recently failed to tell doctors that one of its batches had failed the sterility test, so they had their license suspended. Some of the best institutions in the country were using these pharmacies. While situations like this are rare, it's a real concern.

"Of course, if you look at the number of patients who have lost vision due to problems with compounded Avastin, it's a tiny number compared to the number of patients who have been treated with Avastin," he adds. "None of my patients were ever harmed in any of these situations, but it goes to show that there are issues with compounding pharmacies that we do have to take seriously. You want to ensure, to the best of your ability, that your pharmacy is adhering to the guidelines."

"The compounding pharmacy laws are trying to create more oversight," notes Dr. Brown. "That's a great idea; we want to give safer Avastin to our patients. But the downside of the increased oversight is that some pharmacies are now requiring individual prescriptions. We can't provide an individual prescription for every patient to get the drug; it would simply be too difficult. The FDA's role is to protect the U.S. population, so it makes sense to have these new regulations. However, they may end up limiting the use of Avastin and increasing Lucentis and Eylea use—which the insurance companies won't like.

"I do think surgeons should opt for the certified pharmacies," he adds. "Hopefully, the practical concerns being raised by the new laws can be resolved. In any case, every practice should do a lot of due diligence, checking carefully to find out what the pharmacy you're using is doing. Does it test the compounded drug for toxins? For bacterial contaminants? How many times has it had problems? If a pharmacy starts to require prescriptions we'll switch to a different pharmacy, but we'll do a lot of careful checking to make sure the drugs are safe."

Dr. Kaiser agrees. "I think the key is to make sure that the pharmacy that you're buying your Avastin from is certified," he says. "Then, make sure you periodically double-check the pharmacy's status. Finally, make sure your pharmacy checks the sterility of every batch. Pharmacies don't necessarily do this, but they should."

• ***Inspect the drug package when it arrives from the compounding pharmacy.*** "If the package looks like it went through a freeze-thaw cycle, send it back," says Dr. Kaiser. "You wouldn't want to use that batch. If it looks like the packaging is all wet, as if the ice melted, that's a big tipoff."

In the Pipeline

Naturally, more anti-VEGF drugs

are on the horizon. "Another drug with potential is ALG-1001, an integrin antagonist from Allegro," says Dr. Kaiser. "Integrin antagonists use a different approach to angiogenesis. ALG-1001 is interesting because not only does it seem to work as monotherapy, it also appears to work in combination with anti-VEGF. Right now the big question is, should the initial testing be done as combination therapy or monotherapy? It seems to work by itself and have a long-lasting effect, but it takes a little time to get going. Using it in combination with an anti-VEGF drug may be beneficial because you'll get both the immediate wow factor and the long-lasting effect from the new drug."

"Another anti-VEGF agent that's gotten a lot of attention is Allergan's drug, previously known as Darpin, now called Abicipar," notes Dr. Freund. "They had some issues with inflammation, but they're reformulating. That's thought to potentially be a very potent anti-VEGF agent."

New delivery methods are also promising, in particular because they may eliminate the need for repeat injections. "In wet macular degeneration, the next big thing may be sustained-release anti-VEGF treatment, allowing us to do one treatment that lasts a lot longer," notes Dr. Kaiser. "One approach to this is gene therapy, which would cause anti-VEGF to be released indefinitely. Another approach is the Neurotech method, in which you surgically implant genetically altered RPE cells in a little cylinder. They release the anti-VEGF drug for as long as the implant is in the eye. The latter approach seems safer to me, since when the treatment is done you can remove the cylinder. You can't turn off the gene therapy, which is a little concerning. Testing of the Neurotech system is just starting, though, so we probably won't have it for a few years."

One key factor in new drug development will be Lucentis and Avastin going off patent a few years from now. "In 2019 Lucentis and Avastin go off patent, so if you're doing the numbers on whether to go through a drug-approval process you have to look forward," says Dr. Brown. "It takes three to five years to go through that process, and you're probably going to be competing with other cheaper agents at that point—biosimilar Lucentis and Avastin drugs."

The other key factor is creating a drug that can produce better results than the current drugs, which is not an easy thing to do. "We all hope something will be the next big blockbuster, but it's really hard to surpass the data from the previous trials," Dr. Brown points out.

Taking Action

Dr. Freund notes that all of the current options are viable, so the main issue is getting treated in time. "Comprehensive ophthalmologists who aren't treating with intravitreal injections should be aware that we now have some really good therapies and multiple choices," he says. "The key thing is to identify these patients and get them to a physician who can treat them properly. As a retina specialist, there are pros and cons to each drug, but you can't really go too far wrong with any of the three current drugs for treating macular degeneration. They all work well." REVIEW

Dr. Freund is a consultant for Genentech, Bayer and Regeneron. Drs. Kaiser and Brown are consultants for all of the companies whose products are mentioned.

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Increasing Options to Treat Vein Occlusion

Michelle Stephenson, Contributing Editor

First-line treatment is typically an anti-VEGF agent. If that is inadequate, steroids can be initiated, either in combination with the anti-VEGF agent or alone.

When treating branch or central retinal vein occlusion, the standard of care is pharmacologic therapy with either an anti-VEGF agent or steroid alone or in combination. "For branch retinal vein occlusion, people are mainly using Avastin off-label or Lucentis on-label," says Antonio Capone Jr., MD, a surgeon from Royal Oak, Mich. "For central retinal vein occlusion, we are using those same two drugs plus Eylea and Ozurdex. In patients who would benefit from a steroid, but cost is a consideration, some use triamcinolone off-label instead of using Ozurdex."

Chicago-based surgeon Seenu Hariprasad, MD, points out that only two pharmacologics are Food and Drug Administration-approved for use to treat all retinal vein occlusions: Ozurdex (dexamethasone intravitreal implant) and Lucentis. Eylea (aflibercept intravitreal injection) is also FDA-approved, but only for the treatment of central retinal vein occlusion.

Dr. Capone says deciding on a drug is done empirically: "You try one class of drug to see if it works. If it doesn't, you try the other. If it only works partially, you combine them. There is considerable individual variability with regard to response. The knee-jerk reflex nowadays is to go with an anti-VEGF agent first. If that doesn't work at all, switch to a steroid. If it works partially, the general practice is to switch to another anti-VEGF agent, seeking a better response in a given individual. After that, we'll try steroids either alone or in combination."

Both Lucentis and Avastin have been shown to effectively treat retinal vein occlusion and have similar visual and anatomic outcomes. A recent retrospective study included 81 patients with retinal vein occlusion and macular edema who were naïve to anti-VEGF therapy.[1] Twenty-six eyes were treated with ranibizumab (Lucentis), 33 eyes were treated with bevacizumab (Avastin), and 22 eyes were treated with bevacizumab and then switched to ranibizumab. The main outcome measure was change in visual acuity at three months, six months and at the final visit.

The mean visual acuity improved from 20/80 to 20/40 in the ranibizumab group and from 20/125 to 20/60 in the bevacizumab group. The mean change in central subfield thickness was -186 µm and -212 µm, respectively. The mean time between injections was 94 ±21.1 days in the ranibizumab group and 103.8 ±10.5 days in the bevacizumab group. In

the group that switched from bevacizumab to ranibizumab, mean initial visual acuity was 20/125. Visual acuity reached 20/60 at crossover and remained at 20/60 through the remainder of the study.

Dexamethasone intravitreal implants have also been shown to be a safe and effective treatment option. A recent study evaluated the safety and efficacy of one or two treatments over 12 months in eyes with macular edema related to branch or central retinal vein occlusion.[2]

This study included 1,256 patients with vision loss caused by macular edema associated with retinal vein occlusion. At baseline, 421 patients received a dexamethasone 0.7-mg implant, 412 received a dexamethasone 0.35-mg implant, and 423 received a sham implant. At day 180, patients could receive a dexamethasone 0.7-mg implant if their best-corrected visual acuity was less than 84 letters or if their retinal thickness was greater than 250 µm, and 997 patients received this implant. Except for cataract, the incidence of ocular adverse events was similar in patients who received their first or second dexamethasone implant. Over 12 months, cataract progression occurred in 90 of 302 phakic eyes (29.8 percent) that received two dexamethasone implant 0.7-mg injections compared with five of 88 sham-treated phakic eyes (5.7 percent). Cataract surgery was performed in four of the 302 (1.3 percent) phakic eyes that received two implants and one of 88 (1.1 percent) eyes that received the sham implant.

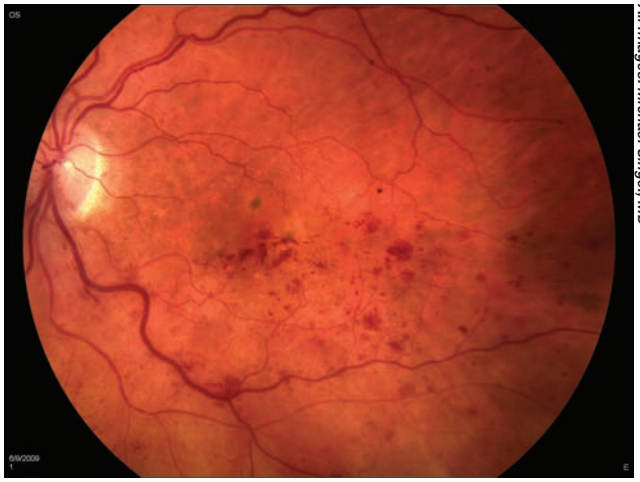

Figure 1. Fundus photo of branch retinal vein occlusion.

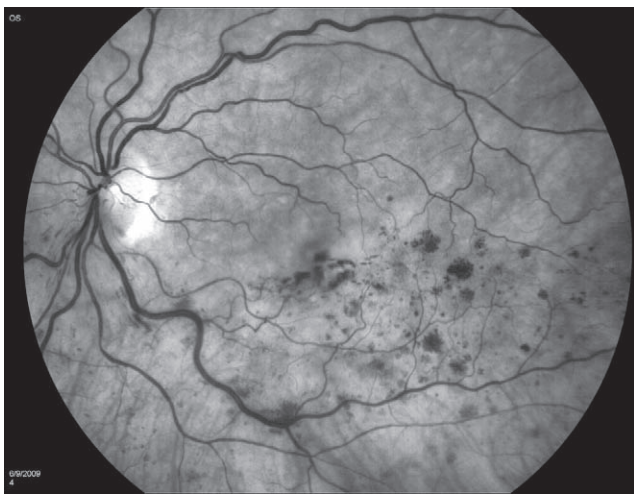

Figure 2. Red-free image of branch retinal vein occlusion.

All images: Michael Singer, MD

An improvement in best-corrected visual acuity of 15 letters or more from baseline was achieved by 30 percent of patients 60 days after the first dexamethasone implant and by 32 percent of patients 60 days after the second dexamethasone implant.

Dr. Hariprasad believes combining pharmaceuticals is very advantageous. "There are some patients in whom I go straight to a combination approach, and there are other patients who are suboptimal responders in whom we will try combination therapy," Dr. Hariprasad says.

A recent study found that bevacizumab combined with dexamethasone implants produced greater improvements in macular thickness than bevacizumab therapy alone and required fewer bevacizumab injections in cases of both branch and central retinal vein occlusion.[3]

The study included 30 eyes that were randomly assigned to receive either combination therapy or monotherapy with bevacizumab. All patients received intravitreal bevacizumab at baseline, followed one week later by dexamethasone implants or sham injections. Monthly bevacizumab injections were given if the central subfield thickness was less than 250 µm, and the combined group received a second implant after four or five months if the central subfield thickness was less than 250 µm.

At six months, patients receiving combined therapy required fewer bevacizumab re-injections compared to those receiving monotherapy (two versus three). The combined therapy group also experienced greater mean reductions in central subfield thickness (-56 µm versus +45 µm) and were more likely to have resolved all edema, which was considered a central subfield thickness less than 250 µm (seven of 11 eyes versus two of 14 eyes). Mean visual acuity changes from baseline were similar between groups.

Dr. Capone notes that many ophthalmologists stick with anti-VEGF monotherapy longer than they should. Typically, patients' response to anti-VEGF injections is evident early in the course of treatment. "Patients who are going to have a good response to anti-VEGF will typically do so within the first three injections,"

he says. "In fact, I think you can tell after the first injection whether the patient will be a marginal responder or a nonresponder. There is a tendency to keep whipping the horse three or six times before deciding to make the switch. This is not in the patient's best interest. The longer the edema is present, the worse the final visual outcome."

He believes that a better approach is to use an anti-VEGF agent and promptly gauge by the presence and magnitude of a response whether the patient should be treated exclusively with an anti-VEGF or whether a steroid should be brought in. "A decision can be made earlier in the game than is conventional practice as to whether an adjunctive or alternative therapeutic agent would be appropriate for a patient with vein occlusion that is only partially responsive or largely unresponsive," Dr. Capone says.

Los Angeles-based surgeon David Boyer, MD, agrees. "If patients don't have the response that I would like, I add the steroids very early," he says. "Other ophthalmologists like to wait until after four, five or six injections. If I'm not seeing the response I want after a couple of injections of anti-VEGF and I add a steroid, it doesn't mean I'm not going to use anti-VEGF after that, but I can add a steroid for a better response."

Michael Singer, MD, from San Antonio, Texas, typically initiates treatment with Lucentis in cases of branch retinal vein occlusion because he conducted a study that found that ranibizumab appears to have a greater effect than bevacizumab in the short-term of decreasing macular edema.[4]

This retrospective study included 64 patients with retinal vein occlusions. Half received injections of bevacizumab, and half received injections of ranibizumab. Central macular thickness and best-corrected visual acuity were obtained at baseline, at two weeks (just prior to the dexamethasone intravitreal implant), and at six weeks. At the two-week examination, the bevacizumab group had a mean central macular thickness reduction of 26.2 ±3.4 percent compared with a 47 ±3.5 percent reduction with ranibizumab. At six weeks, there was a 31.6 ±3.2 percent central macular thickness reduction with bevacizumab versus 52 percent ±3.2 percent with ranibizumab. At two weeks, 15 (9 percent) bevacizumab patients and 25 (78.1 percent) ranibizumab patients achieved a central macular thickness of less than

300 µm, and at six weeks, 18 (56.3 percent) bevacizumab patients compared to 30 (93.8 percent) ranibizumab patients achieved a central macular thickness less than 300 µm. Visual acuity was not significantly different between the two groups at any time interval.

"I like the results of this study because vein occlusion patients are a lot younger than macular degeneration patients as a general rule, and they need better vision sooner," Dr. Singer says. "With central retinal vein occlusion, it gets a little more complicated. If it's more ischemic, I'm much more likely to use Eylea, because the GALILEO and COPERNICUS studies included central retinal vein occlusions in their study design, so aflibercept's effectiveness has been shown.[5,6] The CRUISE study[7] excluded these patients based on the inclusion criteria for the study, so ranibizumab's effectiveness has not been demonstrated in a clinical trial setting," Dr. Singer adds.

According to Dr. Boyer, triamcinolone has been shown to be helpful in central retinal vein occlusions, and Ozurdex has been shown to be helpful in both central retinal vein and branch retinal vein occlusion. "We usually start with an anti-VEGF drug, and if I get a great response, meaning that it dries out and vision improves, then I probably would continue the anti-VEGF, hoping that I could eventually get to a treatment and extend protocol and eventually not need to treat the patient," he says.

Surgical Treatments

According to Dr. Capone, there has been a rise and fall of interest in the surgical management of venous occlusion, whether it is branch retinal vein occlusion with arterial venous sheathotomy, or central retinal vein occlusion with radial optic neurotomy. However, these approaches have not withstood the test of time.

Dr. Hariprasad believes that focal laser treatment has a role in the treatment of branch retinal vein occlusion, but its use in central retinal vein occlusion is more controversial. "If focal laser treatment is not working, we always have vitrectomy surgery with internal limiting membrane peeling in our back pocket as a last resort," he explains.

A recent study has shown that the combination of Ozurdex and macular grid laser is synergistic in increasing best-corrected visual acuity and lengthening the time between injections in patients with branch retinal vein occlusion.[5]

Another treatment option for branch retinal vein

(continued on page 62)


Multimodal Imaging in Plaquenil Toxicity

Advanced imaging techniques may lead to timely diagnosis and more effective treatment of hydroxychloroquine-related toxicity.

Ehsan Rahimy, MD, and James Vander, MD, Philadelphia

Hydroxychloroquine, sold under the brand name Plaquenil (Sanofi-Aventis), is an antimalarial drug that has gained widespread use in treating various autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis.[1] By some estimates, more than 150,000 patients are on long-term therapy with this medication in America alone.[2] Retinal toxicity associated with HCQ use is relatively rare, estimated at 1 percent after five years and rising with continued therapy.[3] However, the retinopathy, described as a bull's-eye, is untreatable and tends to progress even after cessation of the drug. Accordingly, in recent years there has been an increased emphasis on more effective screening measures utilizing multimodal imaging techniques to elicit early signs of toxicity before the characteristic advanced changes manifest clinically. This review summarizes the clinical presentation of HCQ retinopathy, current American Academy of Ophthalmology recommended screening guidelines and contribution of ancillary imaging studies in establishing a timely diagnosis.

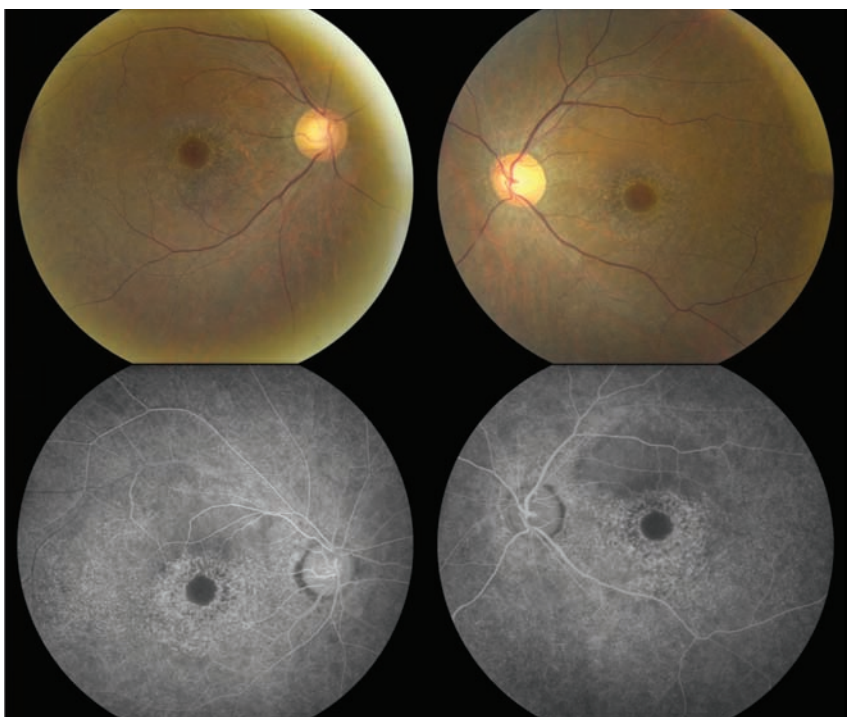

Figure 1. Fundus photos (top) demonstrate extensive paracentral depigmentation of the retinal pigment epithelium sparing the central fovea bilaterally, consistent with bull's-eye maculopathy. Fluorescein angiography (bottom) shows parafoveal granular hyperfluorescence correlating to patchy RPE disruption with subsequent window defect.

Clinical Presentation & Exam

In the earliest stages of HCQ toxicity, patients are often asymptomatic with preservation of visual acuity. However, perceptive individuals may report difficulty with night vision,

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glare or paracentral scotomas that interfere with reading.[4-6] The scotoma typically becomes apparent to the patient well before changes are seen on examination. While recognition of subtle foveal depigmentation has been described in some cases of early toxicity, this was only after corroboration with ancillary imaging studies.[7]

On the other hand, visible bull's-eye retinopathy, characterized by a ring of retinal pigment epithelium degeneration often sparing the foveal center, is a late finding indicative of advanced damage *(See Figure 1)*. Thus, ophthalmoscopy alone is not sufficient to screen for HCQ toxicity.[7,8] That being said, a detailed anterior and posterior segment examination to assess for corneal verticillata as well as concurrent macular disease (i.e., age-related macular degeneration), remains important in monitoring these patients long term.

Screening Guidelines

In 2002, the AAO published its initial *Preferred Practice Patterns* for HCQ retinopathy screening in response to the diverse regimens being advocated at the time.[9] These recommendations were revised in 2011 to reflect the increased sensitivity of newer diagnostic imaging techniques.[4]

If a patient was deemed a low risk for retinopathy, follow-up examinations were recommended beginning at five years of therapy after the initial baseline. If a patient was high risk, annual follow-up was recommended. High risk was defined as someone with duration of HCQ use more than five years, more than 1,000 grams of cumulative consumption, more than 6.5 mg/kg/d daily dosing, increased age (no cut-point specified), concomitant hepatic/renal disease or pre-existing maculopathy of another etiology.[4]

In addition to an ophthalmologic examination and automated threshold Humphrey visual field testing with a white 10-2 pattern (which should be interpreted with a low threshold for abnormality and with repeat testing if irregularities are noted), at least one of the following supplemental objective imaging studies is recommended: 1) spectral-domain optical coherence tomography; 2) fundus autofluorescence; or 3) multifocal electroretinography, at baseline and annually at each visit after five years of HCQ use.[4] Notably absent, fluorescein angiography was not recommended in these guidelines. While FA can reveal the bull's-eye pattern of granular hyperfluorescence and may be able to elucidate subtle RPE defects, it has not been proven to be as sensitive as the aforementioned tests and comes with added morbidity due to its invasiveness.[4]

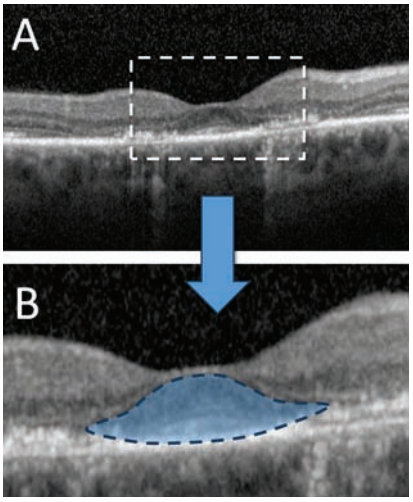

Figure 2. Spectral-domain optical coherence tomography demonstrating advanced hydroxychloroquine retinopathy with parafoveal loss of the external limiting membrane, disruption of the outer ellipsoid zone, thinning of the outer nuclear layer and disruption to the underlying retinal pigment epithelial layer (A). The relative sparing of the subfoveal structures results in the characteristic "flying saucer" sign of advanced toxicity (B).[11]

Spectral-Domain OCT

By generating high-resolution, cross-sectional images of the retina *in vivo*, SD-OCT may detect significant structural alterations prior to development of visible HCQ retinopathy. Previously described OCT findings in HCQ toxicity include loss of the external limiting membrane, disruption of the outer ellipsoid zone, parafoveal thinning of the outer nuclear layer and RPE damage.[6,7,10] Despite these various changes, numerous studies have supported the notion that relative "foveal resistance" is common in HCQ toxicity, as demonstrated by preservation of the subfoveal outer retinal layers, accounting for the intact central visual acuity that can be seen even in advanced disease states.[6] This foveal sparing serves as the basis for the "flying saucer" sign of HCQ retinopathy described by Eric Chen, MD, and colleagues, where an ovoid appearance is created by the intact central foveal outer retinal structures contrasting to the adjacent perifoveal loss of the photoreceptor ellipsoid band and ONL atrophy *(See Figure 2)*.[11]

While much of the literature has focused on the changes to the outer retina in HCQ retinopathy, the earliest SD-OCT findings of toxicity may actually localize to the inner retina. Sirichai Pasadhika, MD, and colleagues observed selective thinning of the perifoveal inner retina on SD-OCT, especially the inner plexiform and ganglion cell layers, in patients treated with long-term HCQ (more than five years) in the absence of structural changes to the outer retinal/RPE or other clinically evident toxicity.[12] Interestingly, thinning of the retinal nerve fiber layer was not found in these patients, which the authors proposed only happens once significant retinal ganglion cell degeneration has occurred. In a separate study designed to compare

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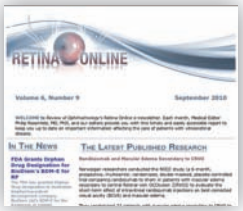

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chronically treated patients with and without ophthalmoscopic evidence of toxicity, significant thinning of the inner, outer and full thickness retina was observed in patients with clinically apparent retinal toxicity, whereas only selective thinning of the inner retina was detected in the group without fundus changes.[13] Once again, RNFL thinning was absent in patients with chronic HCQ exposure and no fundus changes; however, the group with fundus changes related to drug toxicity demonstrated peripapillary RNFL thinning. Recently, Ulviye Yigit and coauthors corroborated these findings by measuring significant thinning of the inner retina during HCQ therapy, especially in para- and perifoveal areas, in the absence of clinical fundus changes.[14] Unique to their study was the inclusion of the patients receiving HCQ treatment for less than five years (average duration: 2.5 years).

More investigations involving larger numbers of patients need to be performed to better determine what SD-OCT-based indices may be reliably assessed in early HCQ toxicity. However, given its rapid image acquisition time, noninvasive nature and wide availability in many clinics, the majority of practitioners continue to favor SD-OCT as the primary adjunct to visual field testing in HCQ screening.

Fundus Autofluorescence

Imaging with FAF may help elucidate toxic alterations to the underlying RPE due to long-term HCQ therapy. An increased FAF signal typically indicates accumulation of lipofuscin, in particular the A2E fluorophore, within the RPE either from abnormal metabolism with increased phagocytosis of photoreceptor outer segments or an inherited/acquired defect of the phagocytotic processes.[15,16] An extinguished FAF signal, on the other hand, indicates RPE cell death.[17]

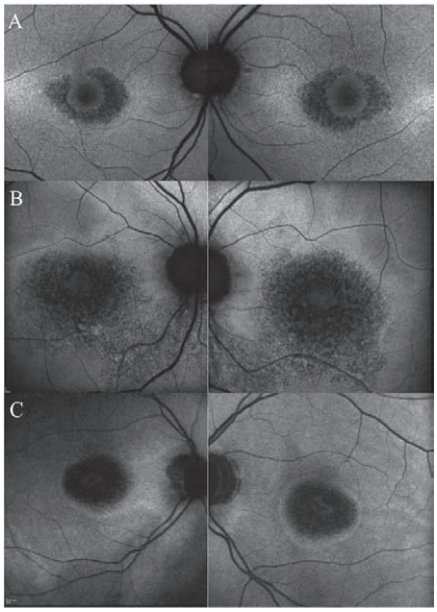

Figure 3. Fundus autofluorescence patterns in various stages of hydroxychloroquine retinopathy. Classic bull's-eye maculopathy appearance (A). As the RPE atrophies, the FAF intensity in the pericentral macula changes to a mottled, or speckled appearance (B), and eventually coalesces into dark areas of absence of FAF signal once the cells have died (C). These dark regions may be bordered by a rim of increased autofluorescence (A-C), portending which RPE cells will undergo degeneration next.

The early finding of a pericentral ring of increased FAF intensity, appearing as a hyperfluorescent glow, may be seen in HCQ toxicity before RPE degeneration develops, and is thought to represent areas of early photoreceptor damage from accumulation of outer segment debris.[4,18,19] However, this can be quite subtle and may be easily missed by the untrained reviewer. When observed, coexisting mfERG or SD-OCT abnormalities have also been concomitantly detected, suggesting a pathophysiologic basis for the FAF finding.[7,18] Despite this, evidence supporting the usefulness of FAF in detecting early subclinical toxicity is still lacking overall, thus making it less reliable as a primary screening tool.

More important than screening, the true value of FAF lies in its capability to monitor progression in known cases of HCQ retinopathy, such as when a patient has been discontinued from the medication, but still requires periodic follow-up examinations. In this context, FAF provides a sensitive indicator of RPE degeneration as toxicity progresses, particularly in advanced stages. As the RPE atrophies, the FAF intensity in the pericentral macula changes to a mottled, or speckled appearance, and eventually coalesces into dark areas of absence of FAF signal once the cells have died *(See Figure 3)*. These dark regions may be bordered by a rim of increased autofluorescence, portending which RPE cells will undergo degeneration next.[17] It bears noting that not all cases associated with advanced retinal atrophy as confirmed by other techniques (i.e., SD-OCT) have a marked appearance on FAF. This finding highlights the importance of the AAO's guidelines to use more than one imaging modality when identifying HCQ toxic effects.

Multifocal Electroretinography

Traditional full-field electroretinography represents a test of global retinal function in response to photic stimulation. As it is not sensitive to functional changes localized to the macula, cases of HCQ toxicity would demonstrate abnormalities only after diffuse retinal damage has already occurred, limiting its utility in screening programs.[4,9]

Conversely, multifocal ERG, with its ability to record localized central retinal defects, has gained acceptance as an excellent candidate for detecting subtle changes in the early stages of toxicity.[20] Raj Maturi, MD, and colleagues first reported a

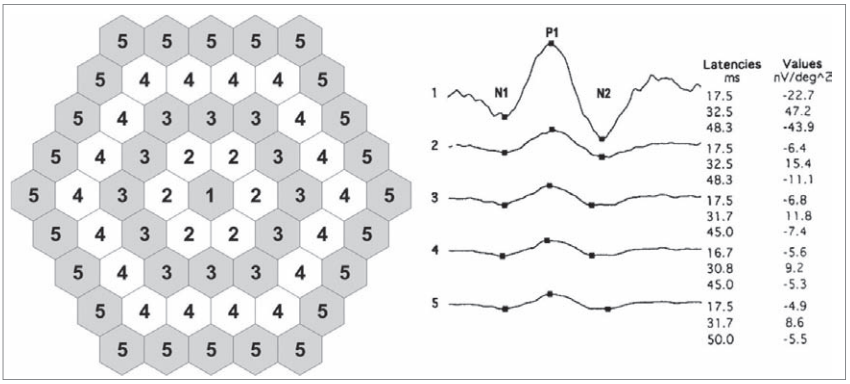

Figure 4. The ring ratio method of multifocal electroretinogram interpretation. The diagram of the 61-hexagon stimulus pattern system on the left shows the hexagons belonging to each ring. Ring-averaged waveforms from a normal patient are on the right. *(See endnotes for image credit.)*

marked reduction in the central 16° mfERG amplitude in a patient with manifest HCQ retinopathy in the setting of a normal full-field ERG.[21] Similar results have been obtained by subsequent studies characterizing HCQ users. Timothy Y.Y. Lai, MMedSc, MRCS, and colleagues observed a longitudinal decline in the retinal function of patients receiving long-term HCQ, and proposed that serial mfERG may help detect early retinal changes associated with toxicity.[22] In a follow-up study, they showed that mfERG responses correlated with the HVF 10-2 mean deviation values, and thus could supplement visual field testing by providing an objective measurement of retinal function in patients using HCQ.[23]

The most specific waveform pattern seen in patients with HCQ toxicity is paracentral amplitude loss, indicative of decreased retinal function in the susceptible perifovea. In another study, Dr. Maturi and colleagues proposed that prolonged implicit time, when seen in conjunction with the paracentral loss of amplitude, may be a more specific feature of HCQ toxicity.[24] Furthermore, they demonstrated three additional configurations, besides paracentral loss, of abnormal mfERG amplitude changes: 1) central foveal loss; 2) peripheral loss; and 3) generalized loss.[24] Their system for classifying patterns of mfERG changes has since been corroborated by other groups.[20,22]

In an effort to increase the sensitivity over standard mfERG interpretation in detecting early HCQ toxicity, Jonathan S. Lyons, MD, and Matthew L. Severns, PhD, developed a novel algorithm for tabulating mfERG data, termed the "ring ratio method" *(See Figure 4)*.[20,25] Given that the amplitude of any single administered mfERG can vary by up to 30 percent from a subsequent testing,[26] the ring ratio was designed to decrease this background noise and create more normative values to aid in clinical decision making. For this, the data from a 61-hexagon mfERG is structured into five zones of concentric rings (R1-R5).

The ring ratios of the mfERG are defined as the ratios of the central ring amplitude (R1) to each of the peripheral ring amplitudes, resulting in five measurements for each eye: R1, R1/R2, R1/R3, R1/R4, and R1/R5. Because R1 has the highest ring amplitude in the normal eye, normal ring ratios are more than 1.0; however, since the areas of depressed mfERG amplitude in HCQ toxicity are typically pericentral ring-shaped, and the central macular area is usually spared until late in the disease process, these patients typically demonstrate a larger ring ratio than would be expected (above the 99 percent limits of accepted normals created from a subset of healthy subjects).[20]

While mfERG testing has shown great promise as an objective measure for detecting early HCQ toxicity as well as tracking the progression of macular changes in known disease, it is limited by its dependence on patient cooperation, specialized staff training for administration and interpretation, and overall cost. Perhaps most importantly, it is not as readily available or easy to reliably perform as SD-OCT or FAF, thus limiting its widespread use to date.

No Single 'Best Test'

Despite the increased integration of these imaging systems into both research and clinical practice forums, there remains no consensus which test is the gold standard for detecting early HCQ toxicity. The discord is evident throughout the literature, as various proponents have argued in favor of visual fields, FAF, mfERG or SD-OCT as the most sensitive/specific method. In a recent retrospective, private-practice based study of 219 patients, David J. Browning, MD, PhD, concluded that the revised guidelines emphasizing ancillary FAF, SD-OCT or mfERG, have actually raised screening cost without improving case detection of toxicity.[27]

Meanwhile, others have suggested that certain patients may differ in their apparent sensitivity to different tests, and therefore careful screening with multiple modalities is likely to increase the diagnostic yield in detecting toxicity prior to the onset of irreversible structural/functional loss.[7] Michael Marmor, MD, and Ronald Melles, MD, re-

cently illustrated the need for this multifaceted approach in a subset of 11 patients representing 10 percent of their patients with known HCQ toxicity. This cohort demonstrated pathognomonic 10-2 field loss with prominent parafoveal ring scotomas that were strongly indicative of retinopathy; however, they did not display any evidence of structural damage on SD-OCT imaging.[28] The authors emphasized the need to take a broad approach when dealing with HCQ screening, not to rely solely on any single procedure, and follow-up any equivocal results with additional confirmatory testing.

Future Directions

The advent of adaptive optics imaging has enabled visualization of the cone photoreceptor mosaic *in vivo* to resolutions of ≤ 2 µm by compensating for aberrations in ocular optics.[29-31] Using this technology, photoreceptor abnormalities have been uncovered in various retinal diseases that were not otherwise discernible with SD-OCT imaging.[32,33]

The use of adaptive optics in HCQ retinopathy is relatively new. Kimberly E. Stepien, MD, and colleagues demonstrated disruption of the cone photoreceptor mosaic in areas corresponding to HVF 10-2 defects and SD-OCT ellipsoid zone abnormalities in two patients on long-term HCQ therapy.[33] Similarly, Korean researchers observed a disrupted cone mosaic pattern with individual cones having irregular shapes and sizes in a patient with bull's-eye maculopathy.[34] Additionally, overall measured cone densities were diminished in all predetermined test points at various distances from the foveal center. Taken together, both groups proposed AO provides a non-invasive, quantitative, high-resolution modality for imaging HCQ retinopathy patients, and may allow detection of subclinical abnormalities that precede objective visual field loss. Larger scale studies are required to validate these findings.

Recently, two groups have described the use of microperimetry systems to evaluate for early HCQ toxicity.[35,36] By testing perimetry under simultaneous fundus visualization, a precise anatomic correlate to a functional aberration can be obtained.[35] Lucia Martinez-Costa and colleagues observed significant differences in microperimetry retinal sensitivity measurements between 209 patients taking either HCQ or chloroquine compared with 204 control subjects.[36] Renu Jivrajka, MD, and colleagues detailed their findings in a cohort of 16 patients on HCQ therapy for more than five years with no signs of toxicity by conventional 10-2 HVF, SD-OCT, FAF or mfERG testing; however, with microperimetry they noted a significant overall reduction in mean retinal sensitivity between patients and age-similar controls.[35] An additional advantage of the particular microperimetry system utilized was its ability to obtain simultaneous SD-OCT images and superimpose retinal sensitivity and thickness values, further reinforcing the notion of correlating functional response to an anatomic structure. Future prospective longitudinal studies are needed, with serial microperimetry testing, in order to better determine whether the reduced retinal sensitivities actually represent early subclinical HCQ toxicity.

Hydroxychloroquine is a valuable drug with an overall low side-effect profile. While ocular toxic effects are infrequent, they may be associated with significant and irreversible patient morbidity. Early detection of toxicity during subclinical stages with discontinuation of the medication may help prevent further structural and functional deterioration. As such, clinicians should maintain a low threshold for suspecting HCQ toxicity. Subtle abnormalities detected using one modality warrant additional follow-up testing to confirm or refute these findings, with the ultimate goal of early diagnosis before irreversible visual loss. REVIEW

Figure 4 reproduced with permission from: Lyons JS, Severns ML. Detection of early hydroxychloroquine retinal toxicity enhanced by ring ratio analysis of multifocal electroretinography. Am J Ophthalmol 2007. May;143(5):801-809.

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(continued on page 55)

A Close Look at Pseudoexfoliation

This disease is linked to vision loss, hearing loss and cataract. Learning more about it may help lead to better treatments.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and James McLaughlin, PhD, Andover, Mass.

Medicinal nomenclature is a curious thing: The systematic logic of Latin-based anatomical identification contrasts with the haphazard terminology used in the naming of diseases. So we call conditions "primary" or "essential" if their underlying cause is unknown, even though "idiopathic" would seem a more appropriate descriptor. Other diseases take on the names of those who first described them, such as Paget's disease or Cushing's syndrome, labels that say more about the condition's history than its etiology. Then there is the wholesale use of the prefix "pseudo," telling us it "looks like this disease, but it's not." Ultimately, we end up with names like pseudopseudohypoparathyroidism, a bone disorder far simpler than its name would imply. These pseudoportmanteaus provide vague clues to the underlying condition, but still leave us wishing for a more descriptive, less verbose designation.

In ophthalmology, all of these elements contribute to pseudoexfoliative syndrome, a condition whose name is at the same time descriptive, historical and yet still a bit misleading. PXS is a systemic condition that first appears in the anterior chamber and can lead to cataract, glaucoma and complications with intraocular surgery. Here, we take a wide-ranging look at what the latest research reveals about PXS diagnosis, etiology, and genetics. We also compare PXS with related disorders and discuss ideas for treatment strategies.

What's in a Name

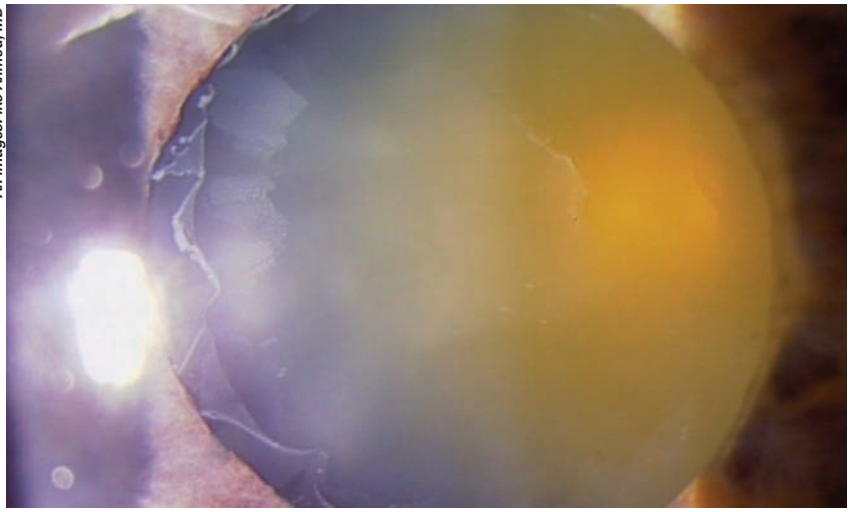
The exfoliation syndrome associated with glaucoma that was first described in 1917 was later referred to as pseudoexfoliation to distinguish it from an occupational condition of "true exfoliation," a delamination of the lens capsule common in glassblowers.[1] In the medical literature of the early 20th century it was sometimes called senile exfoliation, and was considered a relatively rare form of secondary glaucoma restricted to those of advanced years and Nordic heritage. Even as recently as 2000, PXS was described as "a disease primarily of people of Scandinavian descent, with some features that suggest a genetic component."[2] Unlike the black box of primary open-angle glaucoma, it was clear from earliest studies that patients developed glaucoma from PXS as the exfoliative material built up in and around the trabecular meshwork, slowed aqueous humor outflow and caused an elevation in intraocular pressure.[3] While all of this is true, recent studies of the genetic and physiologic mechanisms at work in PXS, together with other glaucoma research efforts, may provide clues leading to real progress in breaking the mechanistic code for POAG.

Diagnosis of PXS

The central finding in a diagnosis of PXS is the presence of white or light flakes in the anterior chamber of the eye, whose resemblance to epithelial debris gave rise to the description as exfoliation. Studies on the nature of the material suggest that it consists of connective tissues (elastin, collagen) together with adhered enzymes.[4,5] Histologically, exfoliation material stains with periodic acid-Schiff reagents, indicating the presence of carbohydrates or proteoglycans. These properties led to the suggestion that the debris included amyloid proteins,

and that it could be related to the central nervous system amyloid deposition that occurs in Alzheimer's disease. It turns out there is no association between the two disorders (although PXS is linked to several systemic conditions; see below).[6,7] While PXS is anecdotally associated with the Scandinavian population, the syndrome accounts for a greater percentage of open-angle glaucomas than primary disease in other ethnic populations, particularly Arabic, Mediterranean and Japanese patients.[4,8,9] Worldwide, it is the most common cause of secondary glaucoma, and represents 5 to 18 percent of all open-angle disease. It's estimated that, globally, 30 percent of people over age 60 have some form of anterior exfoliative deposits.[2]

All images: Ike Ahmed, MD



Fibrillar material on the patient's anterior lens capsule is a hallmark sign of pseudoexfoliation syndrome.

Exfoliation syndrome goes beyond the build up of anterior segment debris. Changes in the lens capsule and iris are also seen in PXS.[1-3] Reduced dilation function due to build up of PXS materials and degeneration of both sphincter and dilator muscles is often observed. In addition, focal membrane disruption in melanin-containing epithelial cells yields a pattern of peripupillary atrophy described as "moth eaten."[2,4]

Collectively, PXS effects in the anterior segment lead to ocular hypertension and open-angle glaucoma. PXS is also associated with increases in angle closure, cataract and lens subluxation. Lens capsule atrophy in combination with poor mydriasis can make for challenging cataract surgery in PXS patients.[2,4] While the combination of IOP-lowering medications and surgical approaches used to treat PXS is the same as that used for POAG, it's possible that a better understanding of this glaucoma variant may lead to more fundamental progress in our knowledge of all forms of the disease.

PXS: A Systemic Disease

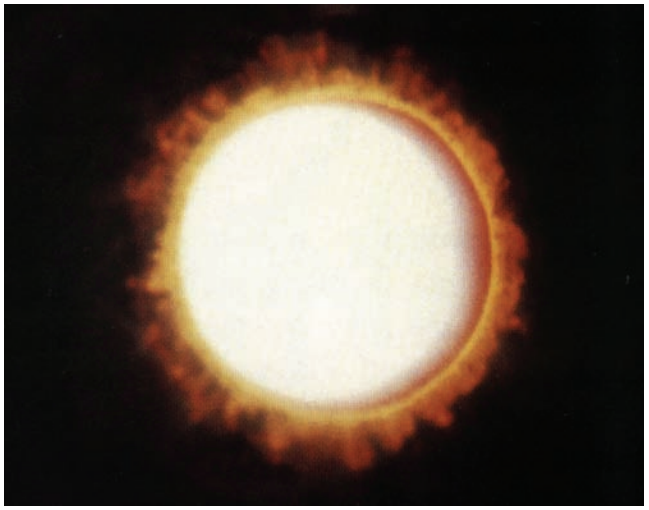
The association of PXS with connective tissue dysregulation is naturally more readily identifiable in the setting of the anterior segment. However, systemic manifestations of PXS have been investigated in both small-scale, retrospective studies and large-cohort, population-based research.[10] As a disorder of connective tissues, particular interest has focused on the potential impact of the disease on cardiovascular function. Despite this interest, the first prospective, case-controlled studies have only been published in the past two to three years. These studies confirm that patients with PXS exhibit higher risk of several common forms of vascular disease, including renal artery stenosis and abdominal aortic aneurysm.[11,12]

Several other conditions have been associated with PXS. An association with sensorineural hearing loss was shown in a study that compared auditory function in PXS patients with age-matched controls.[13] The study examined both frequency range and threshold sensitivities. In contrast, the suggested association between PXS and Alzheimer's disease has been discounted by a number of studies. Interest in this potential linkage stemmed from a desire to identify reliable predictive markers for the degenerative neurological disorder, but several studies have established that no linkage between the two disorders exists.[6,7] Interestingly, a recent report suggested that deposition of β-amyloid in the lens may be the first reliable test for AD.[14]

The association of PXS with connective tissue dysregulation in the eye suggests that it may exert similar effects in other tissues, but for obvious reasons these effects are more readily identifiable in the setting of the anterior segment. Case studies have suggested associations between PXS and skin disorders, pulmonary disease and additional renal conditions. Progress in identifying the genetic loci for PXS is likely to advance investigations into these and other systemic diseases.[15]

Genetics of PXS and Glaucoma

Most of the genes linked to PXS have been identified with genome-wide association studies.[16,17] One of the first such genes encodes one member of a ubiquitous family of enzymes involved in connective tissue metabolism, the lysyl oxidases. The LOXL1 gene product induces crosslinks between different sites on extracellular matrix proteins, and it's



Focal membrane disruption of melanin-containing cells can give the iris a moth-eaten look in pseudoexfoliation.

thought that polymorphisms in the gene associated with PXS encode an altered enzyme resulting in too many crosslinks or inappropriate crosslinks, and ultimately a brittle, more easily damaged matrix.

GWAS have identified the LOXL1 locus as a PXS-associated gene in subjects from diverse genetic backgrounds, further strengthening the case for the gene as a key factor in PXS disease. Despite this, other loci including genes for the extracellular matrix protein, clusterin, the enzyme glutathione transferase and the signaling peptide TNF-α have also been implicated in PXS disease.[8] Other factors, including unilateral presentation and variability in onset suggest that PXS etiology results from the combined effects of genetic predisposition coupled with one or more environmental factors.

Genetics of POAG are complex, and identification of glaucoma-associated genes such as myocilin or optineurin has provided some insight without yielding breakthroughs in either the etiology or treatment of the disease.[18] While identification of genes involved in PXS may provide a clearer pathophysiology for the exfoliative aspects of the syndrome, we are still left with the daunting question of why some develop glaucoma while others do not. While lowering IOP remains the single best predictor of treatment success, patients with normal-tension glaucoma show that there's more to it than that.

Research has found that the common denominator in all glaucoma-linked genes is an association with extracellular matrix and trabecular function, but these same genes may also be participants in homeostasis of the lamina cribrosa matrix. A unifying link, then, is a common effect on the extracellular matrix at both the front and the back of the eye.[19,20]

Changes in the signaling pathway regulated by TGFβ is another aspect of glaucoma pathophysiology seen in pseudoexfoliation and in all other forms of the disease. Patients with glaucoma of any etiology exhibit elevated aqueous humor TGFβ, a cytokine that both regulates matrix formation and causes increases in IOP.[20, 21] Consistent with this role of TGFβ are two genetic disorders: Marfan syndrome and congenital scleroderma. Both of these conditions are due to a mutation of the microfibril-associated gene FBN1, both exhibit elevated TGFβ and both include glaucoma as part of the spectrum of their phenotypes. A recurring question in all of these observations regards cause and effect: Are elevated cytokines and elevated intraocular pressure responses to altered matrix dynamics, or are they somehow the initiators of these responses?

Putting PXS Pieces Together

Another intriguing piece of this puzzle is the phenomenon of normal-tension glaucoma, patients who exhibit the optic nerve head degeneration of glaucoma without an elevation in IOP. A growing body of evidence implicates a mismatch in trans-lamina cribrosa pressures in NTG.[22,23] For some patients, normal ocular pressure could still yield differential pressures across the LC similar to those in patients with elevated IOP, if these patients had unusually low intracranial pressures. One condition in which this pressure difference at the LC may be an issue is idiopathic intracranial hypertension, a diagnosis associated with morbid obesity that is increasing worldwide.[24] For patients with IIH, severe headache and optic disc swelling are the primary diagnostic features. These individuals have cerebrospinal fluid pressures that exceed normal IOP values. In severe cases, patients may require CSF shunting to reduce intracranial fluid pressures, but these devices typically yield extremely low intracranial fluid pressures, effectively "flipping" the trans-LC pressure differential. Patients with long-term in-dwelling shunts are at increased risk for glaucoma, and there is a recent prospective study showing that NTG patients have significantly lower CSF pressures than either controls or high-IOP glaucoma patients.[25]

One explanation for these observations is that factors such as elevated TGFβ are responses to the pressure differentials sensed at the level of the LC, the trabecular meshwork or both. Elevation of matrix regulatory stimuli may initiate a positive feedback cycle in which remodeling could promote or facilitate cupping, nerve damage and further remodeling. While speculative, this idea is consistent with current therapeutic standards that primarily slow the process down. An interesting idea might be to test a dual

therapy of IOP-lowering agents in combination with antagonists of matrix remodeling factors such as TGFβ or connective tissue growth factor.[26] This combination could, in theory, halt the remodeling cycle, reducing the effects of the TGFβ signaling pathway at both the front and the back of the eye.

This allows us to return to one of those inappropriately named diseases that we touched on earlier in this discussion, Marfan syndrome. Marfan is an autosomal dominant disorder caused by dysregulation of the gene for fibrillin 1, a connective tissue protein. Although it is still in the investigational stage, early clinical data suggest that a family of drugs called sartans (such as losartan) that are classified as angiotensin antagonists may be effective in reducing risk of aortic aneurysm, the major risk in patients with this syndrome.[27] In addition to their action on the Renin-Angiotensin system, these drugs also act as physiological antagonists of TGFβ. For Marfan patients, the drug presumably attenuates excessive matrix synthesis in the walls of the great arteries. Patients with PXS, as well as those with POAG, might receive benefit from similar potential actions at the TM and LC. Perhaps calling sartans angiotensin inhibitors is yet another example of where an inaccurate name actually leaves out the most important, and most intriguing, characteristics of the drug. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Dr. McLaughlin is a medical writer at Ora Inc. in Andover.

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The Fluid Wave: Evaluating Canal Surgery

Creating an episcleral venous fluid wave during canal surgery can help surgeons predict the likelihood of success.

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In open-angle glaucoma, the eye's natural outflow channels fail to adequately drain aqueous humor. This increased resistance to outflow causes chronic elevation of intraocular pressure with eventual nerve fiber layer damage and corresponding field loss, the hallmarks of open-angle glaucoma.

For many decades, surgeons lowered IOP by circumventing the abnormal resistance of the eye's inherent drainage system by performing trabeculectomy and creating a new outlet. This surgeon-made artificial outflow track abandoned the eye's natural drain by shunting aqueous to the subconjunctival space, forming a bleb. The potential problems associated with bleb-forming surgery are well known to all ophthalmologists; they include hypotony maculopathy; scarring; dysesthesia; leaks; blebitis; and choroidal hemorrhage.

In recent years, thanks to advances in technology and the relentless pursuit of a better procedure, glaucoma surgeons are shifting away from bleb-forming procedures and moving toward more physiologic operations that enhance flow through the eye's existing drainage system. Instead of abandoning the compromised outflow system, the surgeon and patient choose to try and enhance flow through the native collector system. This bleb-less option is used especially for patients with mild to moderate disease, before their natural collector channels have collapsed or atrophied.

The beauty of this type of microinvasive canal-based surgery is that it improves flow into the patient's own natural drainage system, instead of creating an artificial one. (When explained appropriately, most patients understand the concept of improving flow into their natural drain that's been damaged by glaucoma.) This elegant microinvasive surgery also combines well with cataract surgery, making it possible to achieve two goals with one surgery, without substantially increasing the surgical risk.

Creating a limbal fistula to drain aqueous, as when implanting a filter, typically lowers IOP more than a canal-based procedure, but not every glaucoma patient has advanced disease that requires a subnormal IOP. A significant number of patients could have their glaucoma stabilized if their IOP could be lowered to the level of their episcleral venous pressure.

Despite the advantages of canal surgery, it has a few drawbacks. One major challenge is that it's difficult to predict the success of the procedure. Here, we describe a strategy we've developed that can be used during the surgery to give the surgeon a sense of whether or not the minimally invasive glaucoma procedure is likely to lead to a favorable outcome.

Collector Channels Revisited

There are two major aqueous outflow pathways in the eye: conventional and nonconventional. Conventional outflow is the trabecular meshwork-Schlemm's canal-collector channel path that empties into the episcleral veins; nonconventional outflow is via the uveoscleral pathway (i.e., suprachoroidal). Understanding the anatomy of these outflow pathways is key to understanding how the newer glaucoma surgeries work *(See Figure 1).*

Many surgeons are not well-acquainted with the conventional collector channels, probably for a couple

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of reasons. For one thing, you can't easily visualize the collectors at the slit lamp during a clinical exam. Also, because canal surgery hasn't been a common approach to treating glaucoma for many decades, there has been less need to pay attention to the collector channels. In the 1960s, the advent of trabeculotomy created excitement about angle surgery and spurred extensive research and discussion. However, segmental trabeculotomy with a metal trabeculotome, as invented by H. Mermann Burian, MD, and Lee Allen, MD, didn't produce favorable long-term outcomes, so interest and excitement waned. The technology simply wasn't as good as what we have today.

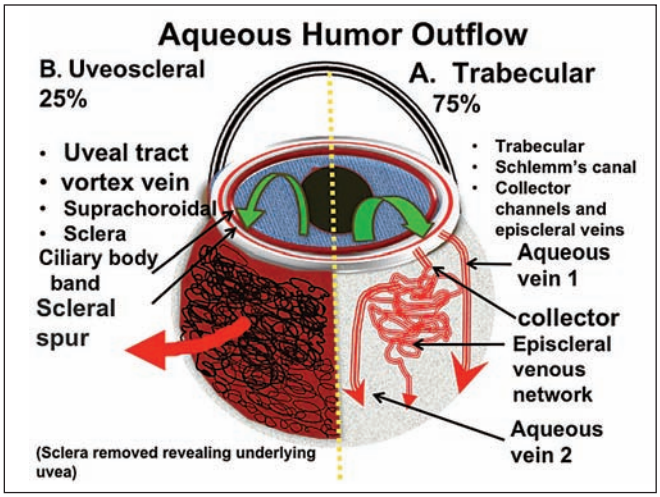

Figure 1. The trabecular meshwork-Schlemm's canal-aqueous episcleral venous outflow pathway is illustrated on the right; the uveoscleral or suprachoroidal outflow pathway is illustrated on the left. Microinvasive canal surgery is dependent on the integrity of the trabecular meshwork, collector channels and downstream venous network for favorable outcomes.

Ultimately, interest in the natural drainage channels plummeted when trabeculectomy was invented. This new surgery allowed surgeons to make a hole in the eye and create a new, nonphysiologic drainage channel, abandoning the patient's natural collectors. After creating an external new drainage pathway, it was not as important to focus on the episcleral veins or collector channels. As a result, much of the science relating to the collector channels ground to a standstill, and their role in glaucoma therapy was slowly de-emphasized and eventually forgotten.

Today, however, canal-based surgeries are experiencing a renaissance. As a result, the collector channels have become a topic of interest again. However, our understanding of Schlemm's canal, the distal collector system and wound healing in the angle lag far behind our understanding of trabeculectomy, glaucoma drainage tubes and wound modulation with anti-metabolites. Hopefully, this new focus on minimally invasive glaucoma surgery will provide greater insight into the canal and distal collector systems.

What Can Go Wrong

The purpose of canal surgery is to optimize the traditional conventional outflow pathway by shunting fluid into the collector channels and out through the episcleral veins. One problem with this approach has been that it's very difficult to assess the preoperative, intraoperative or postoperative condition of the collector channels and episcleral veins. (For example, Matthias C. Grieshaber, MD, evaluated the collector channels with dye during canaloplasty and found that the degree of dye dispersion into the veins correlated with a lower postoperative IOP.[1]) Generally, if the surgery fails to produce the desired outcome, we've had to resort to guessing what the reason might be.

In contrast, with trabeculectomy there is a visible outcome marker: the bleb, which enables the surgeon to better understand why the procedure was successful or failed. If one visualizes a diffuse bleb and it correlates with a low IOP, it makes sense. If the IOP is elevated and a bleb is not present, one understands why the procedure failed. With canal-based surgery, the only marker we have is the postoperative pressure; if the pressure is low, we assume the collectors are working, but we don't have any way to know for sure. That's especially true when we do phacoemulsification at the same time, because it's conceivable that the lowered pressure was a consequence of the cataract surgery.

If canal surgery fails, granted the above limitations, there are several possible reasons:

• ***The stent you placed didn't end up next to a functioning collector channel.*** Unfortunately, the flow of aqueous around Schlemm's canal is limited. That means we can't expect to lower IOP simply by getting more fluid into the canal; we have to get it into the canal at points where there are nearby viable collector channels. That's still a challenge because we don't have any easy or definitive way to determine the location of the collectors.

• ***The collector channels have atrophied.*** One of the things that can go wrong in the eye's natural drainage system is loss of the collector channels. This might happen, for example, if ongoing high IOP caused the trabecular meshwork to be constantly pushed against the back wall of Schlemm's canal where the collectors are located, shutting them off, resulting in downstream channel atrophy. If you were to place an

iStent next to atrophied collector channels, the result would likely be disappointing. Even if the surgery itself went perfectly, the fluid would have nowhere to go and the IOP would remain elevated.

In an ideal world, we'd have some way to evaluate the patency and capacity of the collector channels before deciding to do canal surgery, but at the moment no such method exists.

• ***The stent is malpositioned.*** There is a learning curve for all ophthalmic procedures. After insertion of a device, it may be malpositioned and therefore not functioning correctly. However, it can be difficult to determine whether the device is properly placed.

• ***Scarring has blocked the flow.*** If the IOP drops after the surgery and then climbs back up a few weeks or months later, the issue is most likely wound healing. Unfortunately, the reality is that we're not able to modulate wound healing in the canal at this point in time. This is partly because we can't see what's happening; we don't know if the collectors are closing down. And it's not necessarily a simple thing to do; it took about 60 years to understand how to modulate wound healing with trabeculectomy so it didn't scar down—and in some cases it still does anyway. We're in our infancy trying to understand wound healing in the canal and collector channels, and that puts us at a disadvantage.

The overall problem for us as surgeons is that all of these issues are difficult, if not impossible, to evaluate.

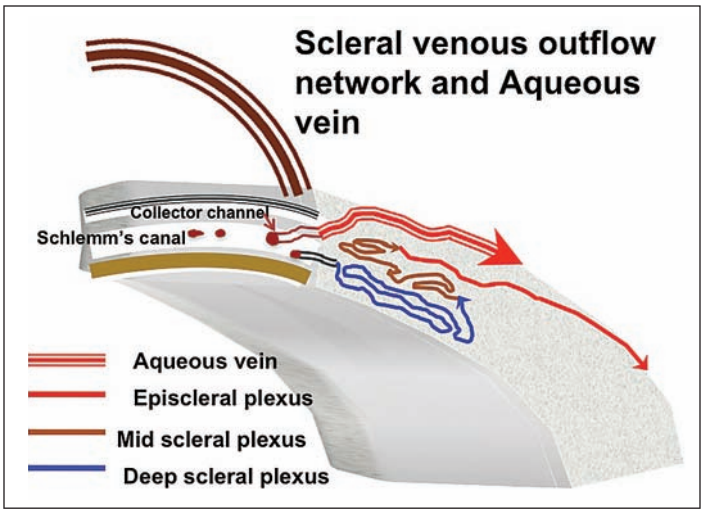

Figure 2. This diagram depicts the route of aqueous humor once it leaves Schlemm's canal. Aqueous must pass through the collector channels to the deep scleral plexus (blue), then to the mid plexus (brown), finally arriving at the episcleral plexus (red). We are currently unable to visualize this pathway preoperatively. However, we can see episcleral flow during surgery (assuming the intrascleral pathway is intact) by visualizing the episcleral venous wave. Note: The large laminated red vein—an aqueous vein of Ascher—originates from the canal and bypasses the entire intrascleral network (deep and mid). This large vein can often be seen postoperatively at the slit lamp and usually correlates with low IOP.

That's where the episcleral venous fluid wave comes in; observing this wave near the end of surgery may provide real information about whether the device is properly located (or the Trabectome has been performed correctly) and the anatomic condition of nearby accessed collector channels, via the clock hours and the extent of the wave. The characteristics of the episcleral fluid wave may help predict the outcome of the procedure, and may suggest the reason for success or failure.

Collector System Anatomy

The human eye has 25 to 35 circumferential collector channels. Approximately six of these collectors are connected to large venous emissaries: the aqueous veins of Ascher. The majority of these larger veins are located nasally and inferiorly, especially inferonasally. That location is fortuitous, because most canal procedures are performed in the nasal quadrant using a temporal approach.

The collector channel system is intricate and difficult to evaluate. It runs through what is called the scleral plexus, which is fairly complex and contains several layers that aqueous must pass through to reach the episcleral veins; the exception is a major vein of Ascher, which has a direct route from the canal to the episcleral vein *(See Figure 2)*. The layer on the bottom is called the deep scleral plexus; the one in the middle is the mid-scleral plexus; and the one on the top is the episcleral plexus. At the slit lamp you can see the channels in the episcleral plexus because they're close to the surface, but you can't see the others because they're deeper in the sclera. Because we're not able to visualize the majority of the collector system, it's very difficult to study and evaluate.

One exception to this is the previously mentioned aqueous veins of Ascher, larger drainage collector channels first discovered in the 1950s by Norman Ascher, MD. While it's not possible to see aqueous moving through most veins in the sclera, it is possible to see aqueous mixing with blood *in vivo* at the slit lamp in the larger aqueous veins of Ascher. And if you were able to place a stent next to one of these channels, it's likely the surgery would produce more favorable results.

The Fluid Wave Explained

The episcleral venous fluid wave is

a transient blanching of the episcleral vessels adjacent to a canal-based surgical site, seen during irrigation and aspiration, first described by us during a phacotrabectome surgery.[2]

Creation of the episcleral venous fluid wave is all about generating pressure differentials. Normally, the pressure in the episcleral veins is around 15 mmHg. If one stops the infusion of balanced salt solution during irrigation and aspiration, the intracameral pressure drops to about 2 or 3 mmHg. The resulting pressure differential encourages blood to reflux from the collector system into the anterior chamber through the canal, specifically in areas where the trabecular meshwork has been bypassed or ablated. If the infusion of BSS is then restarted, there's a rapid reversal of the pressure gradient; BSS will flow out through the path of least resistance, which is usually the collector channels underlying the area of trabecular meshwork that has been cleaved or stented. This surge of BSS washes the blood into the downstream collector system and creates a blanching of the episcleral venous plexus *(See Figure 3, above)*. When the veins fill with BSS, they either become invisible, or one is able to appreciate a train-track appearance of blood lining the inner-wall of the episcleral veins, representing laminar flow.

This visual change in the presence of the episcleral venous fluid wave tells the surgeon that there is communication between the anterior chamber and the downstream collector system. That means the collector channels are probably patent, even at the levels we cannot see; after all, the fluid has to go through those levels to make it to the visible veins. A good visible fluid wave is a strong piece of evidence that the collector channel system is at least anatomically functional, although there is no evidence of its physiologic function.

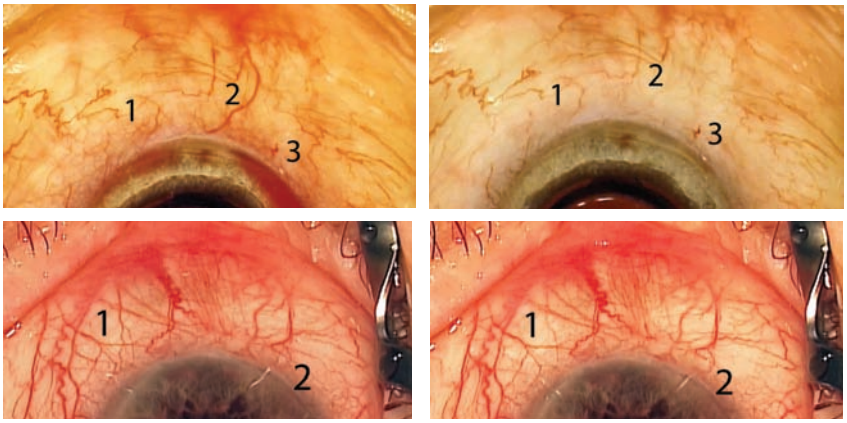

Figure 3. Top: A phacotrabectome case displaying a marked episcleral venous fluid wave. Top left: Baseline view of episcleral veins, no I/A, foot position zero, low IOP. Top right: View of the same episcleral veins with I/A, high infusion, foot position two and high IOP. The high IOP reverses the pressure gradient; BSS flows through the adjacent cleaved meshwork into the veins, washing out the blood. Note how the small veins near numbers 1 and 3, and the large vein near number 2, are far less visible on the right. This case was graded a four-plus wave, suggesting a functioning trabecular outflow system. Bottom: a minimal episcleral venous fluid wave. Left: baseline view. Right: view during episcleral venous fluid wave. Small differences can be seen near numbers 1 and 2, but nothing like the case above. This episcleral venous fluid wave is graded one-plus, suggesting limited function of the trabecular outflow system and the likelihood of a poor outcome for canal-based surgery.

(Of course, if you tried to generate the wave during a phacoemulsification procedure without canal surgery, you wouldn't see anything, because an intact canal will not let BSS into the collector channels. The exchange of fluids in the veins doesn't happen unless you've stented or opened the canal to the anterior chamber.)

Using the episcleral venous fluid wave to evaluate the condition of the collector system first occurred to us during viscocanalostomy. We noted that during viscocanalostomy, in which you unroof the canal *ab externo*, it was possible to inject BSS into the canal and see flow into the nearby episcleral veins. That was very exciting, because for the first time we had intraoperative evidence of the patency of the conventional collector system. Sometimes we would see a great deal of flow, sometimes minimal flow. The same thing happened with canaloplasty. When the Trabectome came along, we wondered if we could see the same phenomenon *ab interno*, a more self-contained model for evaluating episcleral flow, much like during the famed outflow cadaver studies of Paul Chandler and W. Morton Grant. Sure enough, we did. We quickly discovered that when you open up a section of the canal with the Trabectome you typically see the episcleral venous fluid wave at those same clock hours.[2]

This has been true for all the canal surgeries we've tried. If we implanted an iStent, we'd see one to two clock hours of flow into the adjacent veins. If we implanted a Hydrus shunt, which covers three to four clock hours of the canal, we'd see an equivalent area of flow. We recently published a technique we developed called gonioscopy-assisted transluminal trabeculotomy, or GATT, in which we open up 360 degrees of the canal using a microcatheter.[3] This resulted in seeing the flow all the way around the sclera.

Of course, this is only true under optimal circumstances. There are cases in which the flow through the collector channels is minimal. That

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may mean one of several things: the distal collectors may be atrophic; in the case of a shunt, the device may be in the wrong location; possibly the back pressure in the veins is excessive; or more likely, there's some other problem we don't yet understand.

One likely reason the wave has not been appreciated until recently is that when we're operating we're always looking at what's going on through the pupil or in the anterior chamber. During cataract surgery you're not looking at the sclera. To observe the presence or absence of an episcleral venous fluid wave, you not only have to perform the test, you also have to make a point of looking at the adjacent episclera.

Real-World Use

We now use the fluid wave to test the patency of the collector channels as part of every canal procedure. Currently, for example, we frequently combine a Trabectome procedure with phacoemulsification. We start the procedure with the Trabectome, then do the cataract surgery. During the irrigation/aspiration portion, while removing viscoelastic, assuming everything is coming along nicely, the limbus and sclera are visualized to see the veins.

Next, we carry out the maneuver to elicit the episcleral venous fluid wave. We go to foot position zero and let the pressure drop, hopefully producing a reflux of blood from the veins. (The reflux spot is the best location to initially look for the wave.) Then we access foot position two, creating a surge of fluid into the anterior chamber. (We raise the BSS bottle height for this part.) The degree, location and extent of the wave are recorded. This adds a couple of minutes to the case. (If you need to, you can elicit the wave multiple times.)

If the flow is four-plus, an entire section of the sclera may blanch during the wave, not just the larger veins. You'll often see a network of tiny veins between the larger veins, which have a reticulated network appearance. If the flow is good, the fluid will also push the blood down these veins, making the whole area briefly turn white. Of course, if your surgery opens the path into one of the three to six veins of Ascher, which likely connect directly to the canal, you may see a large surge of BSS into the vein of Ascher.

We think a four-plus wave is a sign that the patient is going to do well—or at least better than a patient who doesn't have a wave. (We're currently evaluating this.) Seeing a surge of fluid running down those veins means they are anatomically patent. Unfortunately, we can't say with certainty that they're functional, because functional means the aqueous will flow through there under normal physiologic conditions. Forcing fluid through them in the OR is not very physiologic, but it's all we have. We can't see the collectors preoperatively or postoperatively with any regularity, but by using the episcleral venous fluid wave we can at least see them in the operating room.

Riding the Wave

As canal surgery becomes more popular, the episcleral venous fluid wave can help us identify potential problems and give us a sense of whether the surgery is likely to be successful. It provides some information about the patency of the collector channels before we complete the surgery.

In addition, seeing the wave (or not seeing it) can also help the surgeon set appropriate patient expectations. You can tell the patient that you saw a lot of flow going through his collector channels, and that's a good sign; or you might say you didn't see a lot of flow, so you don't know whether or not the pressure-lowering part of the procedure will work.

We think one day we'll have an optical coherence tomographer or some other technology that will allow us to visualize and evaluate the collector channels. When we have that, we'll be able to improve our results with canal-based surgery. We'll be able to tell a patient that her collector channels can be salvaged. Or, we'll be able to say that the patient's distal collectors are atrophic and probably not functional, so we'll do some other procedure, perhaps designed to increase flow into the uveoscleral pathway. If that doesn't work, we'll still be able to fall back on trabeculectomy. Unfortunately, the technology that will let us evaluate the collector system is probably five or 10 years away.

Microinvasive canal surgery is in its infancy, especially compared to trabeculectomy. Over time we'll work out the best way to increase flow into the canal and the best way to modulate wound healing. It took a long time to improve trabeculectomy, and it will take a long time to improve canal surgery. But we think the odds of us improving canal surgery are much greater today because of our technology—and because small-incision cataract surgery works so well in conjunction with this type of canal procedure. REVIEW

Drs. Fellman and Grover are attending surgeons and clinicians at Glaucoma Associates of Texas in Dallas.

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(continued from page 43)

occlusion is short-duration PASCAL macular photocoagulation, which appears to be safe and provide anatomical improvement.[6]

"Right now, surgery is rarely used and is reserved for people who, with chronic treatment over a long period of time, don't respond," Dr. Boyer says. "If we can duplicate the surgery, meaning that a study could be done that shows the benefit of surgery over anti-VEGF therapy, then I think more people would utilize it, but there are risks involved with surgery and no standardization of the treatment. If surgery could be standardized and more reliable with a low complication rate, I definitely think it would be something that we would have to consider."

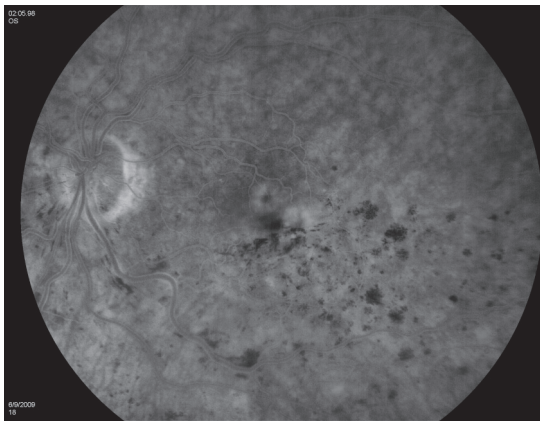

Figure 3. Early-phase fluorescein of branch retinal vein occlusion.

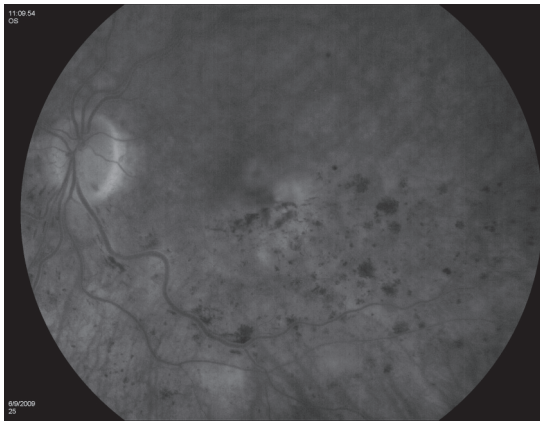

Figure 4. Late-phase fluorescein of branch retinal vein occlusion.

Systemic Treatments

Interestingly, systemic treatment may play a role in resolving macular edema. Three recent cases of macular edema associated with retinal vein occlusion improved after successful treatment of systemic hypertension alone.[7]

The first case was a 72-year-old woman with a central retinal vein occlusion who had macular edema in her left eye and visual acuity of 20/50. Her blood pressure was 169/96 mmHg, and she was prescribed a calcium blocker. One month after the initiation of treatment, her blood pressure was decreased, macular edema was reduced and her visual acuity improved to 20/20.

The second case was a 62-year-old woman with branch retinal vein occlusion. Her visual acuity was 20/40, and her blood pressure was 165/97 mmHg. After six weeks of taking medication to treat her systemic hypertension, the macular edema associated with retinal vein occlusion had decreased and her VA improved to 20/20.

The third case was a 71-year-old man with branch retinal vein occlusion. His visual acuity was 20/50, and his blood pressure was 165/87 mmHg. One month after initiation of treatment for systemic hypertension, his macular edema had disappeared and his visual acuity improved to 20/20.

All of these cases had non-ischemic retinal vein occlusion by fluorescein angiography, and none developed ischemic changes for at least one year.

The authors of this study recommend that blood pressure be measured in all patients with macular edema before initiating treatment with an intravitreal anti-VEGF agent.

Future

According to Dr. Hariprasad, the future of treating retinal vein occlusion looks bright. "There are other sustained-delivery steroid devices that are being investigated, and sustained delivery of steroids and anti-VEGF agents will be a godsend for these patients. We are also looking at wide-field angiography to see if peripheral nonperfusion has a role in the management of this disease," he explains. REVIEW

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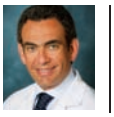


The Keys to Multifocal IOL Centration

How surgeons are meeting the challenge of obtaining the sharpest vision for their multifocal lens patients.

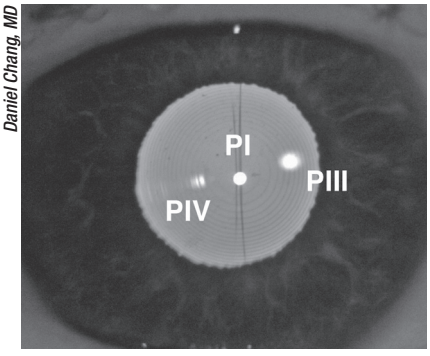
Walter Bethke, Managing Editor

Though diffractive multifocal intraocular lenses can be very successful in some patients, allowing them to see both near and far, surgeons say you'll never achieve such remarkable results unless you get the lens properly centered. The best way to center these IOLs, though, is up for debate, with various surgeons advocating different approaches to getting them positioned properly. Here are a couple of approaches to the problem, and their possible pros and cons.

Thoughts on Centration

Surgeons center their multifocal IOLs based on a variety of factors, ultimately falling back on the process that works best for them.

Des Moines, Iowa, ophthalmologist James Davison bases his centration approach on the pupil and the capsulorhexis. "I don't think you can use any one factor and hope that you'll get it perfect," he says. "And I'm not sure that it really matters to get it perfect. The manufacturers have built in a tolerance so the modulation transfer function of the lens isn't affected even if it's decentered almost up to a millimeter on the bench. Having said that, I'll try to center the lens so that it looks right to me with respect to the dilated pupil at the time of surgery and the capsulorhexis that we made so that it's overlapped completely. I'll rotate the lens so that it sits properly and most of the time I end up leaving [the haptics] superior-temporal and inferior-nasal, with the AcrySof single-piece IOL, at least. I have no data for that at all; it's just that seems to be a good spot for centering that lens in most people. But, if it doesn't look perfect, I'll rotate the haptics to a different location."



Daniel Chang, MD

Bakersfield, Calif., surgeon Daniel Chang says that if you use an instrument with a fixation light that's coaxial to your view, and the patient fixates on it (represented here as PI, or the 1st Purkinje image, shown along with the 3rd and 4th Purkinje images), that will be the best place to center a multifocal lens.

Bakersfield, Calif., surgeon Daniel Chang has been working with Charleston, S.C., ophthalmologist George Waring IV on the concept that an effective centration point would be what they term the subject-fixated, coaxially sighted, corneal light reflex.

"A fundamental problem that we face when addressing the centration of IOL implantation procedures is that we lack consistent nomenclature and a coordinate system with which to discuss the problem," Dr. Chang says. "We use various terms like visual axis, line-of-sight, pupillary axis and optical axis with little regard to their true definitions. Just the term visual axis has multiple usages in the literature. Even if we were to choose a singular definition such as 'the line from the fixation point to the entrance nodal point to the exit nodal point to the fovea,' how does that help me during surgery? The pupillary axis and line-of-sight both are related to the pupil center, but the pupil center shifts when it dilates. Also, the Purkinje reflexes don't always line up, making the optical axis difficult to

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apply when centering a lens.

"Recently, I co-authored a paper with George Waring IV that's now accepted for publication," Dr. Chang continues. "And in it we advocate that the surgeon consider what we call the subject-fixated, coaxially sighted corneal light reflex. That's a mouthful to say, but here's how to understand it: The surgeon looks at the patient's eye through a light such that the surgeon's view is coaxial with the beam path of the fixation light. Then, if the patient's eye is fixated on that same light source, the surgeon sees the reflection of the fixation light as the subject-fixated, coaxially sighted corneal light reflex—everything is lined up. It's a unique lighting situation, and can be seen in various devices already in our practices. The SF-CSCLR is reproducible because it is related to the anterior corneal surface, and it doesn't move around with implant position. Also, though this reflex is actually visualized at the iris/IOL plane, which eliminates parallax, the tricky part is having the patient fixate and using a light that's coaxial with your viewing axis."

At his practice, Dr. Chang did a small retrospective study of 117 Tecnis Multifocal IOL cases centered on the SF-CSCLR with an average follow-up of 100 days. "I looked at the uncorrected and best-corrected vision correlated to centering on the SF-CSCLR vs. centering on the pupil. Though there were trends that showed better vision from SF-CSCLR centration, there were too many other variables and factors for the results to reach statistical significance. Early uncorrected vision, though, suggested better vision trended with centering on the light reflex."

If a surgeon is interested in trying this method of centration, Dr. Chang says the instrument most surgeons have that may let them do it is a placido disc corneal topographer. "I use the Atlas topographer, which has a coaxial fixation light in the center of the rings," Dr. Chang says. "With other topographers, the manufacturer can verify if their fixation light is coaxial with their particular topographer's camera. This would be your preop/postop reference point." Intraoperatively, certain surgical microscopes have coaxial lighting, such as the Zeiss Lumera. "It has three lights, with the two smaller lights coaxial with the surgeon's eyes," Dr. Chang says. "So if you tell the patient to fixate on one of the two stereo coaxial lights, and you look through the ocular on the same side as that light, you have a patient-fixated, coaxially sighted, corneal light reflex. Then, you have an optical arrangement illuminating the eye in the exact same configuration that you did preop and postop; so you have a marker you can correlate preop, intraop and postop." Dr. Chang says it's worth checking with your microscope's manufacturer to see if the fixation light and your viewing axis are truly coaxial.

The next step involves giving surgeons more opportunities to use this centration method, says Dr. Chang. "I'm trying to promote this concept to industry, so we can have more devices that make it easier for surgeons to utilize it," he says.

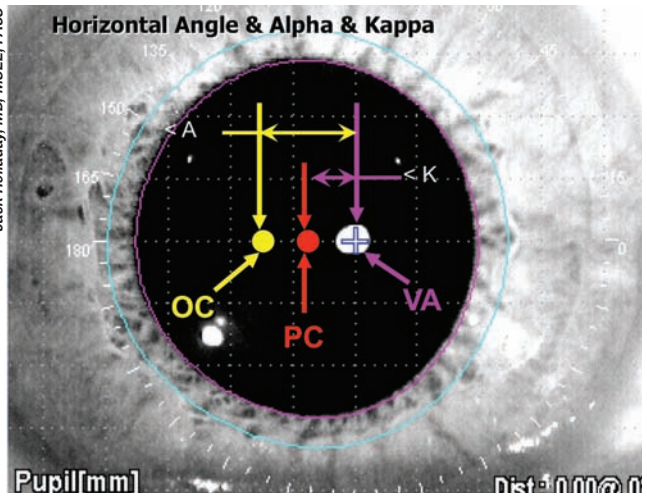
The Other Half of the Story

Houston IOL and optics expert Jack Holladay, MD, MSEE, FACS, says that centering on something such as a corneal light reflex can be helpful with a multifocal lens, but leaves out an important second criterion for getting the sharpest vision.

"For a diffractive multifocal lens to work properly, it requires two things, which usually produces a paradox," explains Dr. Holladay. "First, it has to be lined up so the rays from the cornea are converging so the central ray that comes through the cornea goes through the center of, and is perpendicular to, the lens. In other words, picture two lenses along a common optical axis—they are lined up perfectly. However, when the IOL naturally centers in-the-bag and is aligned with the cornea on the optical axis, both are tilted about 5.2 degrees, called angle alpha, and decentered 0.6 mm temporal to the visual axis and 0.3 mm from the pupil center. This means the lens will always be tilted about 5 degrees relative to the visual axis, so the chief ray coming through the cornea that hits the center of the IOL is never perpendicular and the pencil of light rays never symmetrically converge from the cornea. Because these rays aren't symmetrical and the chief ray isn't perpendicular, they strike the microscopic diffractive edges of the IOL at angles for which they weren't designed. The result is additional light scatter that the patient describes as 'waxy' vision with glare and haloes. If you really wanted to line up the lens so that the central rays were perpendicular to the lens, you'd have to move the lens nasally—almost 0.6 mm nasally—from the center of the bag over to the first Purkinje-Sanson image, or PS1.

"The problem with moving the lens that far nasally, however, is it violates the second requirement of multifocal lenses," Dr. Holladay continues. "The second requirement for diffractive optics is that the lens has to be concentric with the aperture, the pupil. The bifocal or trifocal diffractive optics are only balanced, or symmetrical, when the incoming pencil of rays, or wavefront, are symmetrical with respect to the diffractive rings. This only occurs when the diffractive rings are concentric with the pupil. The imbalance of the resulting diffractive pattern also causes additional light scatter and is additive to the first cause described above. So, unfortunately, it's not possible to satisfy both criteria with the human eye, because the first Purkinje image is almost never centered on the pupil. It's a paradox. The separation between the center of the pupil and the first Purkinje image is called angle kappa, and the best you can do is put

Jack Holladay, MD, MSEE, FACS



OC = the optical center of the cornea; PC = the pupillary center; VA = Purkinje-Sanson I image and visual axis. Houston ophthalmologist Jack Holladay says the ideal place to center a multifocal IOL is between PC and VA.

the lens somewhere between these two points to minimize the additional light scatter and reduce complaints of haloes, glare and waxy vision."

Dr. Holladay says that clinical studies analyzing multifocal IOL results in patients with varying sizes of angle kappa and decentration of the IOL relative to the pupil have confirmed these concepts clinically. "An article by Amar Agarwal and co-workers suggested that patients with large angle kappas—where the center of the pupil and the light reflex are far apart—actually end up with worse performance with diffractive multifocal lenses than patients with smaller angle kappas.[1] A second article confirmed that large angle kappa and decentration of the IOL temporal to the pupil (and farther from the visual axis) were associated with the highest risk of poor outcomes with multifocal IOLs."[2] For the most successful outcomes with diffractive multifocal IOLs, Dr. Holladay recommends that at surgery the IOL be nudged nasally so the diffractive rings are located just nasal to being concentric with the pupil, between the pupil center and the Purkinje light reflex (if coaxial). Secondly, he recommends avoiding patients with large angle kappas (> 0.4 mm or 2.8 degrees when using a penlight or >5.2 degrees on the Orbscan II, which measures about two times larger values).[3] "Following these two rules will avoid the majority of diffractive multifocal patients who are unhappy due to unnecessary glare," Dr. Holladay says. REVIEW

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Not long after a minor accident, a young man presents with swelling and tenderness in his cheek and concurrent tearing.

Brynn N. Wajda, MD

Presentation

A 32-year-old African-American male presented to an ophthalmology office with a chief complaint of persistent swelling and mild tenderness of the right cheek after mild accidental trauma six weeks prior. He described moderate concurrent tearing but denied any change in vision, diplopia, ocular pain, headache or constitutional symptoms including fever, chills or recent weight loss.

Medical History

Medical history was significant only for seasonal allergies for which he had received allergy desensitization injections in the past. He took no chronic medications, and his family history was noncontributory. The patient had moved from Liberia to the United States 20 years prior. He worked as a counselor in a city group home.

Examination

Vital signs were stable and within normal limits. Ocular examination revealed visual acuity of 20/25 in the right eye and 20/30 in the left eye. Pupils were equal and reactive without an afferent pupillary defect. Extraocular motility, confrontation fields and color plates were full in both eyes. Additionally, the intraocular pressure was normal on both the right and left side. Although swelling was evident along the right cheek and lower eyelid, Hertel exophthalmometry was 25 mm on the right and 25 mm on the left with a base of 107 mm. A firm mass was palpable along the right inferior orbital rim that produced some right-sided hyperglobus, and Krimsky testing confirmed no hypertropia *(See Figure 1)*.

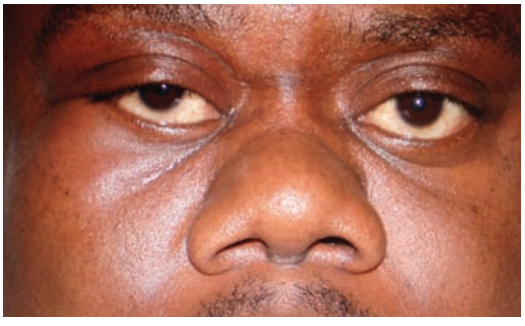

Figure 1. External photograph demonstrating swelling along the right cheek and a mass along the right inferior orbital rim causing hyperglobus.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 72

Diagnosis, Workup and Treatment

Based on the clinical history and exam, the differential diagnosis included inflammatory or reactive conditions such as a hematoma; aneurysmal bone cyst; giant cell or cholesterol granuloma; histiocytosis; and idiopathic orbital inflammation. The differential diagnosis also included infectious and neoplastic disorders such as cellulitis, primary bone lesions (benign or malignant), lymphoproliferative or vascular disorders, and secondary neoplasms including sinus-related lesions or distant metastases.[1,2]

A CT of the orbits was performed and showed an expansile, moth-eaten and osteolytic lesion involving the right zygoma *(See Figure 2)*. With acquisition of these radiographic findings, a more complete and extensive bone-lesion differential diagnosis was drafted. This included benign processes such as osteoid osteoma, osteoblastoma, enchondroma, chondroblastoma; malignant processes such as a primary sarcoma (i.e., osteosarcoma, chondrosarcoma, Ewing's sarcoma), metastasis, myeloma, lymphoma and choristoma; and reactive, fibrous or vascular lesions including aneurysmal or unicameral bone cysts, fibrous dysplasia, osteomyelitis, Langherhans' cell histiocytosis, non-ossifying fibroma and bone hemangioma.[1,2]

The patient underwent an orbital biopsy. Resulting pathology showed sheets of numerous strap cells with abundant eosinophilic cytoplasm reminiscent of rhabdomyoblasts and scattered mitotic figures *(See Figure 3)*. Immunohistochemistry stains were positive for desmin, myogenin, AE1/AE3 and CAM 5.2.

The patient was diagnosed with orbital spindle cell rhabdomyosarcoma and was referred to the Wills Eye Hospital Ocular Oncology service as well as the Thomas Jefferson University Hospital Otolaryngology and Hematology/Oncology departments. A PET/CT showed that disease was localized to the right orbit. While all options, including observation, chemotherapy, radiotherapy and surgical debulking/resection were discussed, the final recommendation was to pursue a combination of systemic and localized therapy in the form of neoadjuvant chemotherapy (vincristine, adriamycin, and cyclophosphamide) followed by local radiation ±local debulking. Unfortunately, after only one visit in each of the previously mentioned departments, the patient refused further therapy and failed to return for any further visits.

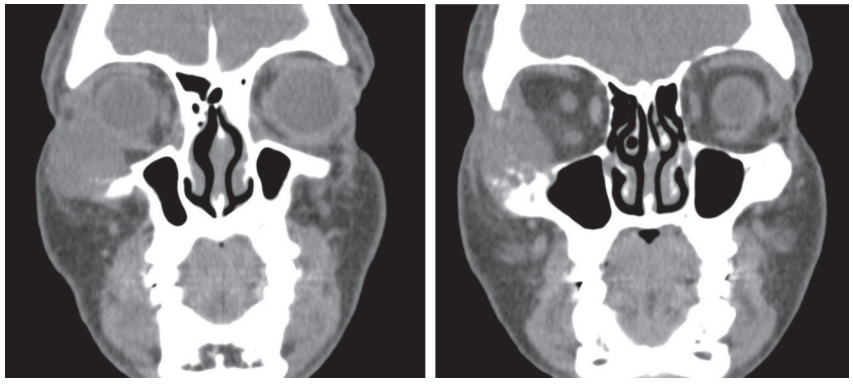

Figure 2. Side-by-side CT coronal images which demonstrate an expansile soft-tissue and osteolytic lesion involving the right zygoma and orbital space.

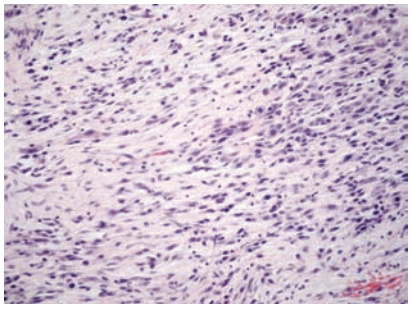

Figure 3. Histopathology photograph demonstrating extensive sheets of strap cells with abundant eosinophilic cytoplasm and mitotic figures.

Discussion

Rhabdomyosarcoma is a neoplasm that develops from undifferentiated mesenchymal cells that have the capacity to differentiate into striated muscle. Based on the widely adopted generalized Horn and Enterline classification system, there are classically four distinct histopathological subtypes, each with its own characteristic and identifying features: embryonal; botyroid variant of embryonal; alveolar; and pleomorphic. Although used in the original Intergroup Rhabdomyosarcoma Studies, in recent years this scheme has been modified and adapted by investigating organizations including the National Cancer Institute with the goal of creating a classification system that would better predict patient outcome.[3]

The embryonal subtype is the most common, with a frequency of 50 to 60 percent and a five-year survival of 94 percent. Within the embryonal category, the botyroid (named for its association with a mucous membrane-like conjunctiva and grapelike clinical appearance) and spindle cell variants are deemed favorable histopathologic subtypes due to their superior prognosis and longer survival rates. Embryonal rhabdomyosarcoma usually arises in the superonasal orbit and thus

produces inferolateral globe displacement. This is contrasted with the alveolar subtype, which histopathologically resembles pulmonary tissue due to branching, fibrous septae that enclose the tumor cells and create pseudoalveoli. The alveolar subtype has an approximate frequency of 30 percent, a five-year survival rate of 74 percent, and usually arises in the inferior orbit. Additionally, around 75 percent of alveolar cases have a characteristic genetic translocation involving chromosome 1 or 2 and chromosome 13 [t(1;13) or t(2;13)]. These genetic variations have prognostic significance, with the t(1;13) mutation having a much more favorable survival rate. Finally, the classic pleomorphic variant is now a subset within the anaplastic rhabdomyosarcoma category used in modern classification systems. It represents less than 1 percent of rhabdomyosarcomas and occurs almost exclusively in adults.[3-8] In addition to histopathology, immunohistochemistry is critically important in making the diagnosis of rhabdomyosarcoma. Some of the most common markers include desmin; myo-D1; myoglobin; myogenin; muscle-specific actin; skeletal muscle myosin; and vimentin.[4,8,9,10]

Orbital rhabdomyosarcoma is most commonly a disease of pediatric patients who usually present with symptoms before the age of 10 years. It represents approximately 4 percent of pediatric malignancies and is the most common soft-tissue sarcoma of the head and neck in this patient population. Initial presenting symptoms usually include rapidly developing proptosis, globe displacement, eyelid edema, and ptosis. In contrast, adult cases such as ours are much more rare. In fact, no more than 20 documented adult cases were found during a literature review spanning a 50-year time period after 1965.iv,v,vi While the orbital location is most common, Carol Shields, MD, found various ophthalmic sites of disease in a 25-year period case review.

Table 1. IRSG Surgical-Pathologic Grouping System

Group	Definition
I	Localized tumor, completely removed with pathologically clear margins and no regional lymph node involvement
II	Localized tumor, grossly removed with (a) microscopically involved margins, (b) involved grossly resected regional lymph nodes, or (c) both
III	Localized tumor with gross residual disease after grossly incomplete removal, or biopsy only
IV	Distant metastases present at diagnosis

Table 1, outlining the intergroup rhabdomyosarcoma post-surgical staging system. *(Adapted from: Raney RB, et al.[10])*

Specifically, 76 percent were located in the orbit, but the conjunctiva, eyelid, and uveal tract were also found to be primary sites of disease.

In terms of staging, categories are classically defined based on the Intergroup Rhabdomyosarcoma Study post-biopsy system *(See Figure 4)*.[11] Favorable prognostic factors include an orbital location, younger age (1 to 10 years), female sex, embryonal histology, and low tumor burden (size <5 cm diameter).[4-6,12]

Treatment approaches usually correlate with the stage of disease. Specifically, patients with stage I disease usually receive chemotherapy with either vincristine or actinomycin. For those with stage II or III disease, some combination of chemotherapy (typical agents being vincristine, actinomycin and cyclophoshamide) and radiotherapy is the standard. Finally, for those with metastatic or stage IV involvement, an intensive chemotherapy and radiation regimen is used, along with intrathecal chemotherapy for patients with intracranial involvement. With advances in chemotherapy and radiotherapy over the past 50 years, surgical treatment is no longer the standard of care, and survival rates have markedly improved from 30 percent to 90 percent. In fact, while surgical excision and exenteration used to be the primary treatment, these approaches are often reserved for cases with recurrent disease.[4,11,13]

In summary, rhabdomyosarcoma is the most common primary orbital and soft tissue malignancy in children, but can occur in patients of any age. Four distinct histopathological subtypes have different frequency rates and prognoses. Fortunately, due to advances in chemotherapy and radiotherapy over the past fifty years, survival rates have markedly improved and disfiguring procedures such as exenteration are no longer the standard of care. REVIEW

The author would like to thank Robert Penne, MD, and Michael Rabinowitz, MD, members of the Wills Eye Hospital Oculoplastic and Orbital Surgery Service, for their time and assistance in preparing this case report.

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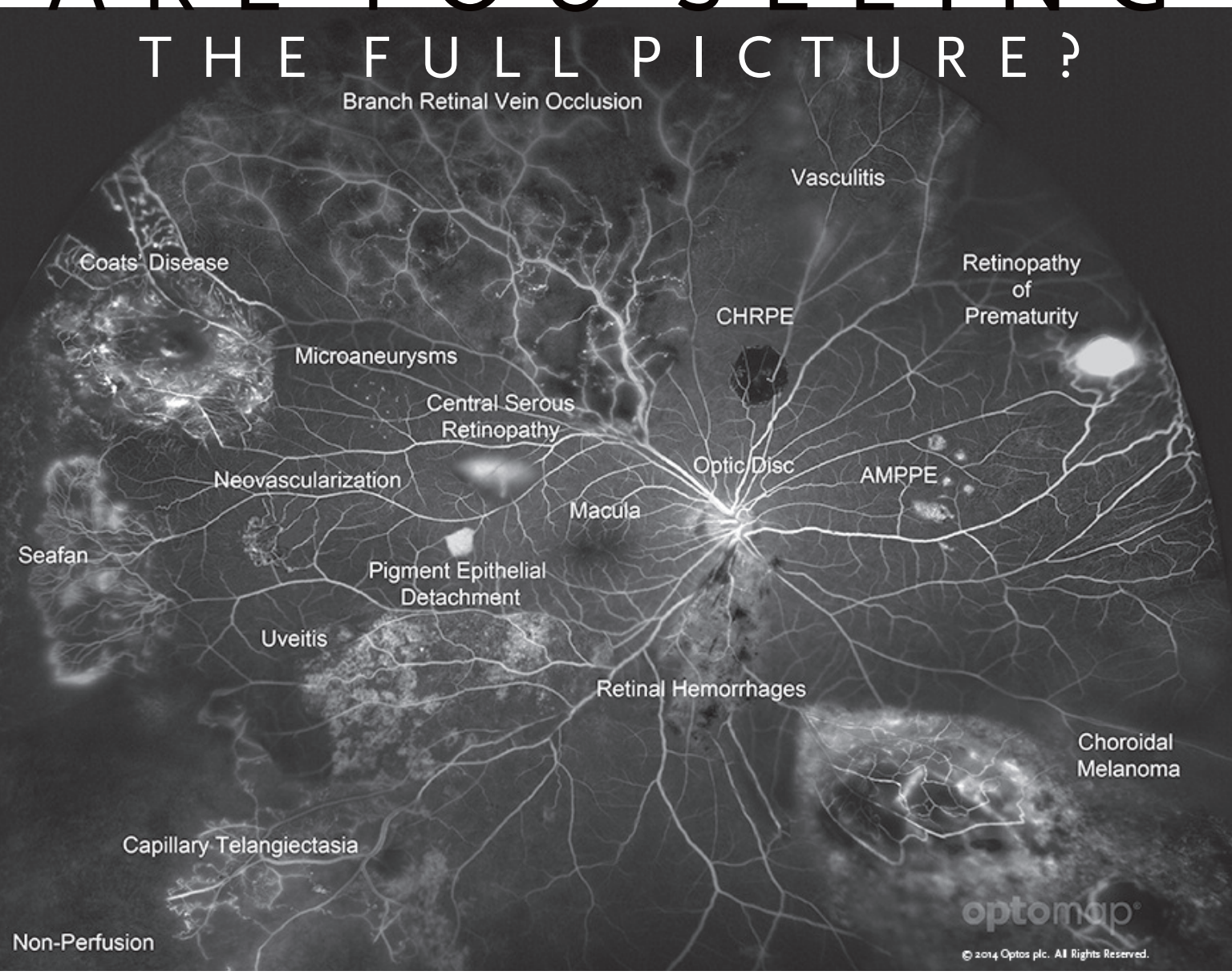

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[1] Kiss et al. Comparison of ultra-widefield fluorescein angiography with the Heidelberg Spectralis® noncontact ultra-widefield module versus the Optos® optomap. Clin Ophthalmol. 2013, 389-94.

2 : Data on file

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