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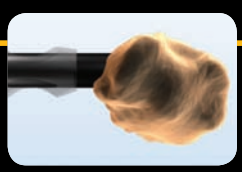

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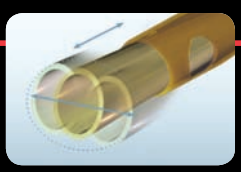

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REVIEW NEWS
Volume XX • No. 11 • November 2013

Cataract Surgeries on the Rise, Raising Access & Cost Issues

As baby boomers enter their retirement years, health-care costs for complex and debilitating conditions such as Alzheimer's disease are expected to soar. Not drawing as much attention is the likelihood of similarly rising expenses for common age-related medical procedures. A Mayo Clinic study looked at one of those—cataract surgery—and found that more people are getting the procedure, seeking it at younger ages and having both eyes repaired within a few months, rather than only treating one eye. The demand shows no sign of leveling off, raising the need to manage costs and ensure access to appropriate cataract treatment, the researchers say. The findings were published in the *Journal of Cataract & Refractive Surgery*.

"Cataract surgery rates are rising in all age groups between 50 and 90, but the greatest increase is in the 70- and 80-year-olds. And part of that is that our older population, or the aging baby boomers, are working longer, they want to be more active, they have more demands on their vision," says senior author Jay Erie, MD, a Mayo Clinic ophthalmologist. "That's why they're looking for surgery sooner — so that they can remain independent, remain active, continue to work."

In the United States, age-related cataracts affect at least 22 million people and cost an estimated $6.8 billion to treat each year; the cataract case load is expected to rise to 30 million people by 2020, the researchers noted.

Despite the common nature of cataracts, the United States has little current population-based data on cataract surgery, information that can help estimate demand. For the Mayo study, researchers mined the National Institutes of Health-funded Rochester Epidemiology Project to identify cataract surgeries in Olmsted County, Minn., from 2005 to 2011. The project, a partnership of Mayo Clinic, Olmsted Medical Center and other health providers, makes the county one of few places worldwide where researchers can examine medical data on virtually everyone to see how often conditions strike and whether treatments succeed.

The research found:

- Cataract surgery has increased steadily, peaking in 2011 at a rate of 1,100 per 100,000 people.
- Sixty percent of people receiving cataract surgery on one eye returned within three months to have it performed on the second eye, a significant increase over the number

TFOS Seeks Formal Definition of Contact Lens Discomfort

Contact lens discomfort may be the leading cause of patient dissatisfaction with, and discontinuation of, contact lens wear throughout the world—but there is little agreement among vision researchers and eye-care professionals about how to define and manage its causes.

"Up to half of all contact lens wearers experience contact lens discomfort," said Jason J. Nichols, OD, MPH, PhD, professor at the University of Houston College of Optometry. "However, there is no global consensus concerning the definition, classification, epidemiology, pathophysiology, diagnosis, management and the proper design of clinical studies for CLD."

To lay the groundwork for defining and treating this widespread issue, the Tear Film & Ocular Surface Society organized the TFOS International Workshop on Contact Lens Discomfort, which was chaired by Dr. Nichols. The findings were reported in *Investigative Ophthalmology & Visual Science*.

The CLD Workshop took 18 months to complete and involved 79 experts from around the world. "Workshop participants used an evidence-based approach and a process of open communication, dialogue and transparency in order to achieve a global consensus concerning multiple aspects of CLD," said Mark Willcox, PhD, FBCLA, FAAO, MASM, professor at the School of Optometry & Vision Science, University of New South Wales, and vice-chair of the workshop.

"This TFOS report will significantly increase awareness of factors that may, and may not, contribute to the generation of CLD. Ideally, this TFOS report will stimulate innovative research in this very important field," added David A. Sullivan, MS, PhD, FARVO, senior scientist at the Schepens Eye Research Institute/Harvard Medical School and Organizer of the TFOS CLD Workshop.

The workshop report is freely available to scientists and clinicians worldwide (tearfilm.org).

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[2]Ophthalmology and Optometry

in a previous Mayo study, which covered 1998 to 2004.

• The mean annual rate of cataract surgery for women was significantly higher than for men.

• There were significant increases in cataract surgery over the past 32 years among people in all age groups, except those 90 and older.

The trend raises questions about treatment costs and the resources needed to meet demand, Dr. Erie says. Medicare, for example, typically covers cataract surgery for its patients; in general, cataract surgery on a Medicare patient costs roughly $3,000 per eye.

"Ophthalmology and ophthalmologists and patients and payers are beginning to look at ways they can weigh the visual benefits to the individual patient against the cost to society as a whole, and how we can maximize the outcome and minimize the cost to society." Dr. Erie says.

New Test Could Diagnose RP

A new Duke University study says it can link what is in a patient's urine to gene mutations that cause retinitis pigmentosa. The findings appear online in the *Journal of Lipid Research*.

"My collaborators, Rong Wen, MD, PhD, and Byron Lam, MD, at the Bascom Palmer Eye Institute in Florida first sought my expertise in mass spectrometry to analyze cells cultured from a family in which three out of the four siblings suffer from RP," said Ziqiang Guan, PhD, an associate research professor of biochemistry in the Duke University Medical School and a contributing author of the study.

Dr. Guan's collaborators had previously sequenced the genome of

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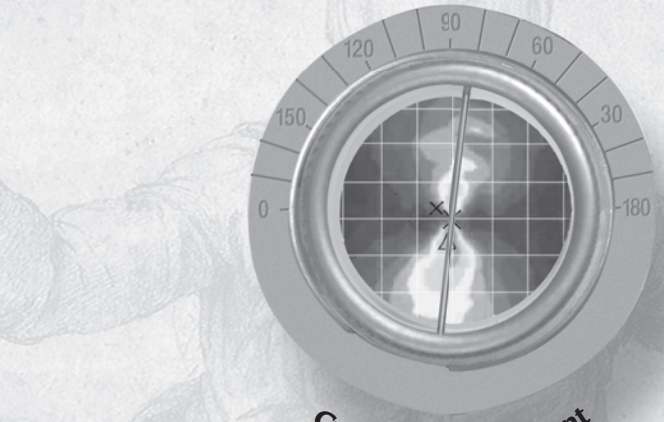

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Ophthalmic Product Development Insights

Matthew Chapin, Brian Campion, Susan Benton, Van Sandwick • Ora Inc., Andover, Mass.

In our previous three columns, we've discussed the steps of establishing a Target Product Profile; when and how to coordinate meeting with the Food and Drug Administration; and developing a business plan in order to secure funding. In this column, we will discuss considerations surrounding intellectual property, or IP, within the context of establishing and protecting market share for the target product.

Protection Strategies

Beginning with the end in mind, one must take care to consider 1) how the target product market share will be protected and 2) whether there is third-party IP that would block the intended manufacture, use, distribution or sale of the target product in the target market. Provided that the target product is well-differentiated by its performance (e.g., efficacy and safety) when compared to substitute products, the most often considered way to achieve market share or exclusivity is through the limited monopoly provided by a granted patent. While outside the scope of this column, it should also be noted that several layers and/or combinations of IP strategies exist for protecting products or services. In addition, a product may be eligible for exclusivity depending on the regulatory pathway followed.

Trade-secret protection may also be used to protect product and service elements where patent protection is not possible or where trade-secret protection is a better choice. Companies will often maintain details of a manufacturing process, formulation know-how, a clinical model or methodology, scales and the like as trade secrets. Effective trade-secret protection strategy requires careful planning and customization depending on the technology and the context in which it is used, including diligent use of confidentiality agreements; a plan within your organization on how information will be shared (or not) and used; and thorough tracking and enforcement. With the proper protection, trade secrets can provide indefinite protection.

Patent Protection

Patents provide the holder with the right to exclude others from making, selling, using and importing the patented drug, device or method for a period of 20 years from filing. The types of patents relevant to this discussion are: 1) Composition of Matter or Device patent, which claims the compound/biologic or device itself; 2) Method of Use patent, which covers the use of compound/biologic or class of the same to treat a disease; 3) Formulation patent, which covers the pharmaceutical dosage form; and 4) Manufacturing patent, which covers the manufacturing process. Many view composition of matter and device patents as the preferred type of patent and it is usually the first type of patent filed for a product. However, it should be strongly noted that one can easily create market share by leveraging the other types of patents, which can extend patent protection beyond the life of a soon-to-expire composition of matter or device patent. In the context of drug rescue or drug repurposing, new method of use patents can sometimes open the door to exclusivity for using a known compound for treating a different disease. This is often seen with ophthalmic therapeutics that are repurposed actives into new topical or locally delivered products, for example antibiotics, anti-inflammatories, anti-allergics and anti-neovascular agents that were previously used for non-ocular indications. Likewise, new formulations of existing compounds can dramatically enhance the safety and efficacy of a chemical entity. Finally, manufacturing patents can be valuable by preventing competitors from utilizing the most cost-effective method for the target product. Once the type of subject matter has been defined, one must look to see if it is patentable.

The two main requirements for being granted a patent are that the invention must be novel and non-obvious. Novelty is a straightforward test that looks to published papers, granted patents, patent applications and other references, collectively referred to as "prior art," to determine whether or not the invention has been described in its entirety in a single publicly accessible prior art reference before the filing date of the relevant patent application. Non-obviousness, on the other hand, is a much more complex test that can be thought of as the next hurdle following a finding of novelty. An invention is deemed to be obvious by the United States Patent and Trademark Office if all of the various portions of the invention are described or suggested in two or more prior art references. Note that while simplified here, application of the obviousness standard can be very complex. With the basics of the standards of patentability in mind, one can get a basic lay of the land, so to speak, by conducting a first-pass prior art or patentability search on PubMed and the USPTO website (or Google under the patents subsection). Sound IP protection will be key in the efforts to raise funds from venture capital or otherwise convince potential partners to invest time and money in commercializing the target product.

Depending on the parameters of your patentability search, one will probably need a freedom to operate search.

FTO Analysis

While patentability speaks to meeting the novelty and non-obviousness standards to obtain one or more patent claims, FTO refers to an analysis of the third-party patent landscape relevant to the target product you wish to bring to market. For example, you may feel comfortable that a new method of use and related formulation is patentable after conducting a patentability search. Such a patentability search would likely not uncover that one or more third-party patents may block the only cost-effective way to manufacture the new formulation on a large scale. A solid FTO analysis is one way to avoid a momentum-destroying surprise later.

The defining features of how the product will be used and manufactured are employed to create search terms for identifying third-party IP, which may preclude selling of your target product in the market. Broadly crafted search terms are well-advised. A good patent attorney will be able to help identify the defining features of your target product, create appropriate search terms and evaluate whether the references in question may preclude you from selling your target product absent a license from the relevant third-party

patent holder. In the event that a third-party patent or patent application is deemed to be different but still close to your target product and it is owned by a large, litigious company, the reality is that weakly supported lawsuits brought by deep pockets can create real problems for entrepreneurs at the point the target product becomes profitable. Moreover, problems can be created at the fundraising stage if the potential investor discovers an FTO issue during due diligence and considers the risk of lawsuit to substantially affect the value proposition for your target product. FTO searches can range in price from several thousand dollars to tens of thousands of dollars depending on the complexity of the target product, how crowded the patent landscape is, and how many references are close to the target product.

The first questions to ask before embarking on a mission to bring a product (whether from scratch or by repurposing) to market are: "Do I have, or is there room for, ample IP protection to establish market share for the target product? And do I have, or is there a path to, freedom to operate in the market as intended?" The answer to these questions will substantially affect your ability to attract suitable investment and partners for development and commercialization of the target product. The importance of understanding the value of your patent estate cannot be underscored enough if you wish to begin with the end in mind.

Other Considerations

The strategy for global filings also needs to be considered with the end partner/investor in mind. Large pharmaceutical partners will generally want and expect worldwide patent filings in the largest eye-care markets, including the United States, Japan, and Europe (at least the big five in the EU), Latin America and other large markets that respect IP. A common issue in the early stage of development is the IP budget, and generally the entrepreneur will need to prioritize the most lucrative markets based on commercial value. Early discussions with potential exit partners are invaluable in this regard.

Consider the scenario in which a pharmaceutical company owns a patent covering, or claiming, the chemical structure of a small molecule that has expired. The company also owns patents claiming methods of using the small molecule to systemically treat various diseases, and those patents will be in force for another 10 years. The method of use patents do not disclose eyedrop formulations of the compound for use in treating ophthalmic diseases, because previous research had suggested it to be non-fruitful due to formulation issues. However, in an inventive moment, an ophthalmologist entrepreneur formulates the compound successfully for animal experiments. The formulation work and experimentation generates surprising results that an eyedrop formulation of the compound is possible (i.e., stable) and that it likely will be efficacious in treating the disease, thus yielding potentially patentable formulation, method of use and possibly manufacturing claims.

Despite the apparent simplicity of the foregoing example, it is important to note that the patent law Doctrine of Inherency is often relevant within the context of repurposing drugs. For example, a patent applicant might not be entitled to a new method of use claim directed to the use of a new compound to treat glaucoma if a prior art reference describes an existing patented compound that is in the same class as the new compound and that operates by the same mechanism of action as the new compound. The reason is that because the existing compound is in the same class and has the same MOA as the new compound, it is inherent that the existing would also treat glaucoma. Therefore, the prior art reference would anticipate (render non-novel) the claim directed to the use of the new compound to treat glaucoma. A formulation claim may still be available in our example as the prior art suggests that formulation challenges exist and that there is room for invention in solving these challenges, provided that the non-obviousness bar to patentability can be overcome.

While the preceding hypothetical purports to open the doors of potential opportunity, be cautioned that (just as with all issues surrounding the complexity of patent law) a competent patent attorney should be consulted at the appropriate inflection points along the way.

Again, it is important to define the target product profile early, identifying how the product will be protected from competition, and to have early discussions with potential partners to define how the IP strategy will impact the value of the product.

The authors comprise the Corporate Development Team at Ora Inc. They thank Andrew Warner, counsel at Ora, for his assistance and input on this column. They welcome comments; for further information, please contact mchapin@oraclinical.com.

(continued from page 5)

this family and found that the children with RP carry two copies of a mutation at the dehydrodolichol diphosphate synthase (DHDDS) gene, which makes the enzyme that synthesizes organic compounds called dolichols. In humans, dolichol-19, containing 19 isoprene units, is the most abundant species.

The DHDDS mutation, which was found in 2011, is the latest addition to more than 60 gene mutations that have been implicated in RP. This mutation appears to be prevalent in RP patients of Ashkenazi Jewish origin, and one in 322 Ashkenazi carries one copy of the mutation.

"I knew from my previous experience in analyzing urine samples from liver disease patients that I can readily detect dolichols by liquid chromatography and mass spectrometry," Dr. Guan said. Using these techniques, he analyzed urine and blood samples from the six family members and found that instead of dolichol-19, the profiles from the three siblings with RP showed dolichol-18 as the dominant species. The parents, each of whom carries one copy of the mutated DHDDS gene, showed intermediate levels of dolichol-19 and higher levels of dolichol-18 than their healthy child. Dr. Guan believes dolichol profiling could effectively distinguish RP caused by DHDDS mutation from that caused by other mutations.

Dr. Guan and his collaborators hope to develop the dolichol profiling method as a first-line diagnostic test to identify RP patients with abnormal dolichol metabolism. They think this mass spectrometry-based detection method will help physicians provide more personalized care to RP patients, especially to young children whose retinal degeneration has not fully developed.

(continued on page 10)

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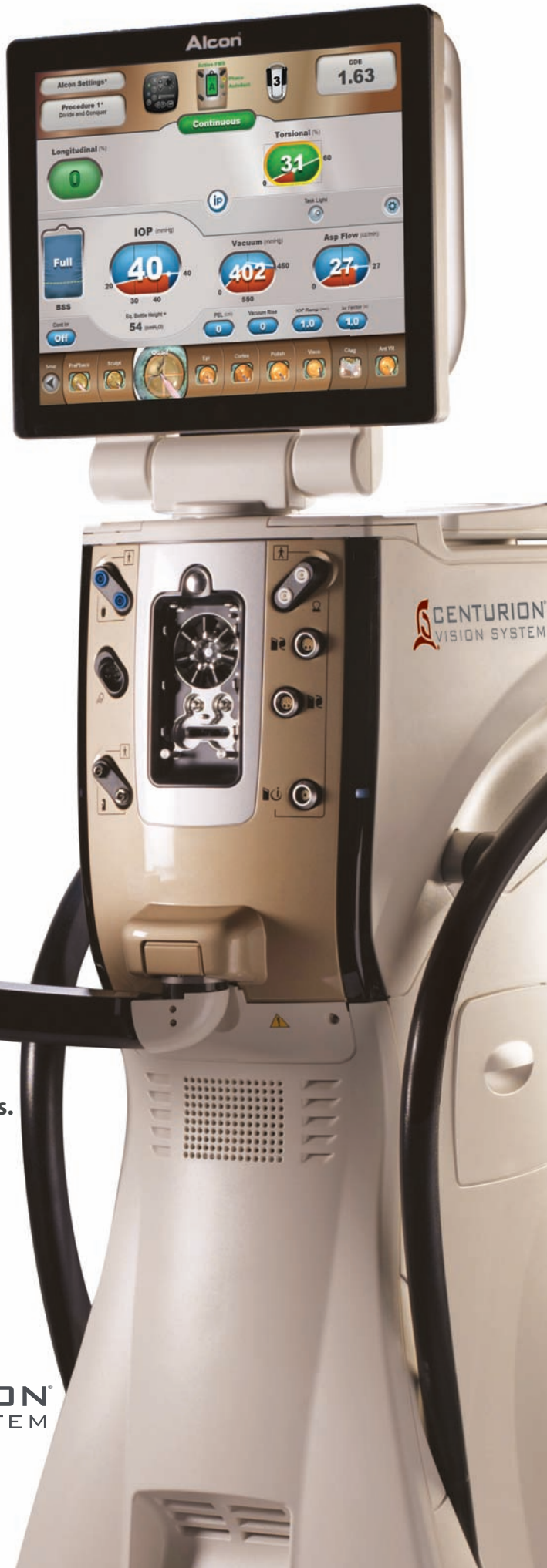

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(continued from page 7)

"Since the urine samples gave us more distinct profiles than the blood samples, we think that urine is a better clinical material for dolichol profiling," he said. Urine collection is also easier than a blood draw and the samples can be conveniently stored with a preservative. The team is now pursuing a patent for this new diagnostic test for the DHDDS mutation.

There are currently no treatments for RP, but Dr. Guan hopes his research will shed light on potential drug design strategies for treating RP caused by DHDDS mutation. "We are now researching ways to manipulate the dolichol synthesis pathway in RP patients with the DHDDS mutation so that the mutated enzyme can still produce enough dolichol-19, which we believe may be important for the rapid renewal of retinal tissue in a healthy individual," he says.

Topical AMD Treatment Shows Promise

Researchers from Tufts University School of Medicine and the Sackler School of Graduate Biomedical Sciences have identified a possible topical treatment for AMD in a study of mice that shows promise for clinical use. The findings, published in *PLoS ONE*, are the first to report successful topical use of a compound capable of inhibiting symptoms associated with both dry AMD and wet AMD and could represent a breakthrough for treatment of these conditions.

The team of researchers from Tufts, led by Rajendra Kumar-Singh, PhD, reported in their proof-of-concept study that topical application of a compound called PPADS (pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid) inhibits damage to ocular tissue that impacts the individual's ability to see color and fine detail, as well as reducing neovascularization related to advanced AMD.

According to the National Eye Institute, more than 7 million people in the United States are at substantial risk of developing AMD. Only the wet form of AMD can be treated, with injections every four to 12 weeks that can be uncomfortable, risky and burdensome to patients. The development of a topical eye-drop treatment that works in both dry and wet AMD could increase treatment adherence and reduce patient discomfort by reducing or removing the need for direct injections.

"An ideal therapy would be one that can be self-administered daily by patients. Further studies are needed to determine safety, dosage, and other factors before advancement of this therapy towards clinical trials, but our study suggests that there's significant promise for the development of self-administered topical treatments for age-related macular degeneration in humans," said Dr. Kumar-Singh, an associate professor of ophthalmology at Tufts University School of Medicine.

To test the effectiveness of a topical application of PPADS, the team of researchers induced the tissue damage and blood vessel growth characteristics of AMD in anesthetized mice. The topical treatment was then administered every 24 hours for three consecutive days. The researchers then examined the eye tissues one week later to assess for progression of the damage and blood vessel growth.

"Our study found that topical application of the PPADS compound works on two fronts" said first author Kerstin Birke, PhD, a postdoctoral scholar at Tufts. "First, it stops the damage to eyes caused by pores formed in the membrane, which leads to cell death within the eye, by stopping an immune system process known as complement, which is responsible for dry AMD. Second, it prevents the formation of the blood vessels that can leak and damage the eye, a process associated with wet AMD." REVIEW

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WARNINGS: Appropriate use of CENTURION® Vision System parameters and accessories is important for successful procedures. Use of low vacuum limits, low flow rates, low bottle heights, high power settings, extended power usage, power usage during occlusion conditions (beeping tones), failure to sufficiently aspirate viscoelastic prior to using power, excessively tight incisions, and combinations of the above actions may result in significant temperature increases at incision site and inside the eye, and lead to severe thermal eye tissue damage.

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ATTENTION: Refer to the Directions for Use and Operator's Manual for a complete listing of indications, warnings, cautions and notes.

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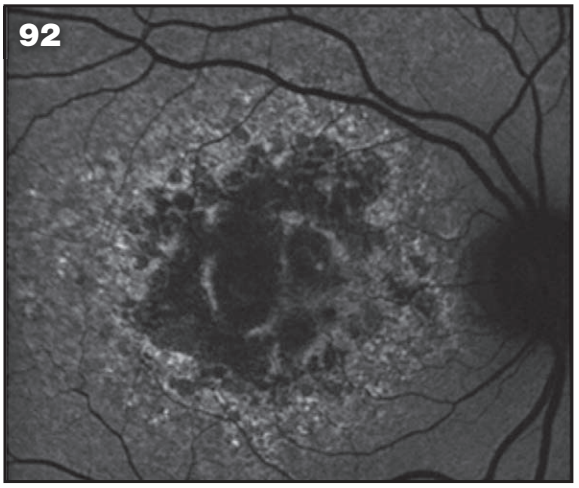

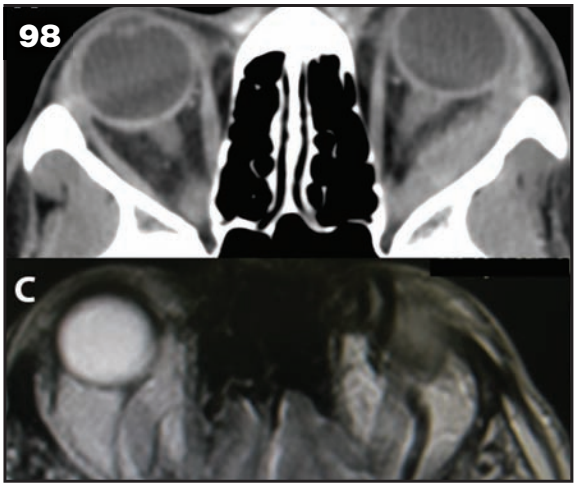

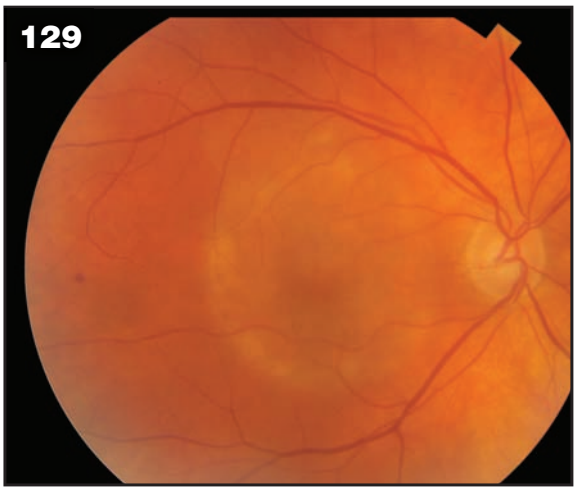

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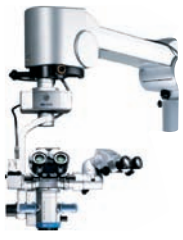

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Not Quite Year's End Has a Feel of Transition

Our Academy of Ophthalmology issue has a different feel this year. Timing is only part of it. Knowing that you'll essentially return from New Orleans and sit down to a turkey dinner tells you that it's certainly later in the year than the norm. While we'll be here in December, we'll have much less to say, far fewer pages to fill. So there something of a finality about this one. But I think it's more a feel of transition to something new that pervades our cover series of features this month.

That change is in the offing in medicine is undeniable, and in this issue we've gathered a series of articles we hope will help you prepare for the New Normal. Whether that's through a bountiful offering of efficiency improvements (p. 26) or a look at some of the ways that you might tap alternate income streams (p. 42), there are ways to fight back.

The next article in the series, on failed EHR implementation and how to avoid it (p. 48), may be reflective of a bigger problem. The article itself is full of sound advice on dealing with an EHR lemon. On a higher level, it turns out there may be something inherently destructive in the idea of putting health-care providers in the position of having to fight back. No one promised you a rose garden in residency, but a Rand Corp. study on physician satisfaction released this week takes particular aim at the role of EHR implementation on physician attitudes and satisfaction.

"EHR usability," the report says, "represents a unique and vexing challenge to physician professional satisfaction. Few other service industries are exposed to universal and substantial incentives to adopt such a specific, highly regulated form of technology, one that our findings suggest has not yet matured. On one hand, only one in five physicians we surveyed would prefer to return to paper-based medical records. Nearly all physicians we interviewed saw the benefits of EHRs ... and believed in the "promise of EHRs." On the other hand, physicians cannot buy, install, and use a promise to help them deliver patient care. The current state of EHR technology appears to significantly worsen professional satisfaction for many physicians—sometimes in ways that raise concerns about effects on patient care."

This too shall pass. Most of the surgeons we talk to find a way to fix what's broken and move on.

On a more positive note, our good friend Dr. Rob Kershner took some time this month to share some his experiences and insights about what the future holds for the profession (p. 66). Finally, while not part of the cover series, the FDA remains an object of fascination and we have an enlightening look at how the agency got where it is and what the prospects are for fixing what's broken there.

Have a great Academy meeting and enjoy your turkey.


Video Screening for Diabetic Retinopathy

A new approach to detection appears to be just as effective as traditional methods, but easier to use—even by non-medical staff.

Christopher Kent, Senior Editor

Like most conditions, diabetic retinopathy is best caught and addressed early in the disease. However, screening for diabetic retinopathy has traditionally required a skilled doctor to take and interpret retinal photographs, limiting the availability of early detection.

Recently, a group in Australia has been conducting studies that suggest a new digital video technique they've developed for diabetic retinopathy screening has specificity and sensitivity equal to that achieved using the standard still-photo method, while being easier to do, providing a larger view of the retina and being less prone to technical failure. Furthermore, the simplicity of the process allows non-medical personnel to perform the test.

Because the resulting digital files are large, the group has also experimented with condensing the files to make them smaller and easier to send and store. That work has found that the files can be condensed to a small fraction of their original size and still produce accurate screening results, comparable to those achieved with traditional retinal photography.

A Different Retinal View

Daniel Ting, MBBS, a PhD student at the Center for Ophthalmology and Visual Sciences at the Lions Eye Institute, University of Western Australia, coauthor of several studies of the technique, notes that traditionally, retinal photography has been the most common method used by primary-care physicians for this type of screening. "Capturing a good quality retinal image is highly dependent on the operator's ability to perform retinal photography, as well as patient compliance with instructions and tolerance of the bright light," he says. "As a result, retinal photography is often performed by highly trained professionals, which makes it less accessible in a remote community. Moreover, even when performed by experienced retinal photographers, the reported technical failure rate of mydriatic retinal photography has been as high as 12 percent.

Daniel Ting, MBBS

A patient is screened for diabetic retinopathy using the EyeScan video system. The technique is reportedly easier to use than standard photography and provides a broader view, while matching the sensitivity and specificity.

"Our method uses

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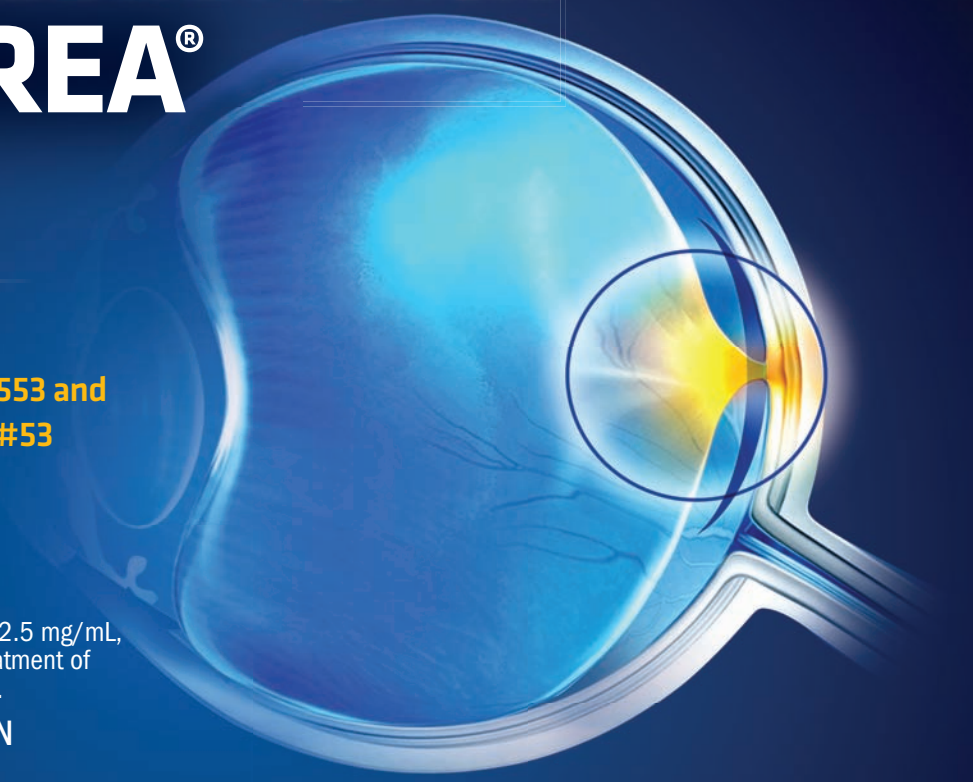

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Indication

JETREA® (ocriplasmin) Intravitreal Injection, 2.5 mg/mL, is a proteolytic enzyme indicated for the treatment of symptomatic vitreomacular adhesion (VMA).

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- A decrease of ≥3 lines of best-corrected visual acuity (BCVA) was experienced by 5.6% of patients treated with JETREA® and 3.2% of patients treated with vehicle in the controlled trials. The majority of these decreases in vision were due to progression of the condition with traction and many required surgical intervention. Patients should be monitored appropriately.
- Intravitreal injections are associated with intraocular inflammation/infection, intraocular hemorrhage, and increased intraocular pressure (IOP). Patients should be monitored and instructed to report any symptoms without delay. In the controlled trials, intraocular inflammation occurred in 7.1% of patients injected with JETREA® vs 3.7% of patients injected with vehicle. Most of the post-injection intraocular inflammation events were mild and transient. If the contralateral eye requires treatment with JETREA®, it is not recommended within 7 days of the initial injection in order to monitor the post-injection course in the injected eye.
- Potential for lens subluxation.
- In the controlled trials, the incidence of retinal detachment was 0.9% in the JETREA® group and 1.6% in the vehicle group, while the incidence of retinal tear (without detachment) was 1.1% in the JETREA® group and 2.7% in the vehicle group. Most of these events occurred during or after vitrectomy in both groups.
- Dyschromatopsia (generally described as yellowish vision) was reported in 2% of all patients injected with JETREA®. In approximately half of these dyschromatopsia cases, there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

Adverse Reactions

- The most commonly reported reactions (≥5%) in patients treated with JETREA® were vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment, and retinal edema.

Please see Brief Summary of full Prescribing Information on adjacent page.

VISIT JETREACARE.COM OR SCAN QR CODE FOR REIMBURSEMENT AND ORDERING INFORMATION

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JETREA™
(ocriplasmin)
Intravitreal Injection, 2.5 mg/mL

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Please see the JETREA® package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

JETREA is a proteolytic enzyme indicated for the treatment of symptomatic vitreomacular adhesion.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Must be diluted before use. For single-use ophthalmic intravitreal injection only. JETREA must only be administered by a qualified physician.

2.2 Dosing

The recommended dose is 0.125 mg (0.1 mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose.

2.3 Preparation for Administration

Remove the vial (2.5 mg/mL corresponding to 0.5 mg ocriplasmin) from the freezer and allow to thaw at room temperature (within a few minutes). Once completely thawed, remove the protective polypropylene flip-off cap from the vial. The top of the vial should be disinfected with an alcohol wipe. Using aseptic technique, add 0.2 mL of 0.9% w/v Sodium Chloride Injection, USP (sterile, preservative-free) into the JETREA vial and gently swirl the vial until the solutions are mixed.

Visually inspect the vial for particulate matter. Only a clear, colorless solution without visible particles should be used. Using aseptic technique, withdraw all of the diluted solution using a sterile #19 gauge needle (slightly tilt the vial to ease withdrawal) and discard the needle after withdrawal of the vial contents. Do not use this needle for the intravitreal injection.

Replace the needle with a sterile #30 gauge needle, carefully expel the air bubbles and excess drug from the syringe and adjust the dose to the 0.1 mL mark on the syringe (corresponding to 0.125 mg ocriplasmin). THE SOLUTION SHOULD BE USED IMMEDIATELY AS IT CONTAINS NO PRESERVATIVES. Discard the vial and any unused portion of the diluted solution after single use.

2.4 Administration and Monitoring

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad spectrum microbiocide should be administered according to standard medical practice.

The injection needle should be inserted 3.5 - 4.0 mm posterior to the limbus aiming towards the center of the vitreous cavity, avoiding the horizontal meridian. The injection volume of 0.1 mL is then delivered into the mid-vitreous.

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

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

Each vial should only be used to provide a single injection for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, and injection needles should be changed before JETREA is administered to the other eye, however, treatment with JETREA in the other eye is not recommended within 7 days of the initial injection in order to monitor the post-injection course including the potential for decreased vision in the injected eye.

Repeated administration of JETREA in the same eye is not recommended *[see Nonclinical Toxicology]*.

After injection, any unused product must be discarded.

No special dosage modification is required for any of the populations that have been studied (e.g. gender, elderly).

3 DOSAGE FORMS AND STRENGTHS

Single-use glass vial containing JETREA 0.5 mg in 0.2 mL solution for intravitreal injection (2.5 mg/mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Vision

A decrease of ≥ 3 line of best corrected visual acuity (BCVA) was experienced by 5.6% of patients treated with JETREA and 3.2% of patients treated with vehicle in the controlled trials *[see Clinical Studies]*.

The majority of these decreases in vision were due to progression of the condition with traction and many required surgical intervention. Patients should be monitored appropriately *[see Dosage and Administration]*.

5.2 Intravitreal Injection Procedure Associated Effects

Intravitreal injections are associated with intraocular inflammation / infection, intraocular hemorrhage and increased intraocular pressure (IOP). In the controlled trials, intraocular inflammation occurred in 7.1% of patients injected with JETREA vs. 3.7% of patients injected with vehicle. Most of the post-injection intraocular inflammation events were mild and transient. Intraocular hemorrhage occurred in 2.4% vs. 3.7% of patients injected with JETREA vs. vehicle, respectively. Increased intraocular pressure occurred in 4.1% vs. 5.3% of patients injected with JETREA vs. vehicle, respectively.

5.3 Potential for Lens Subluxation

One case of lens subluxation was reported in a patient who received an intravitreal injection of 0.175 mg (1.4 times higher than the recommended dose). Lens subluxation was observed in three animal species (monkey, rabbit, minipig) following a single intravitreal injection that achieved vitreous concentrations of ocriplasmin 1.4 times higher than achieved with the recommended treatment dose. Administration of a second intravitreal dose in monkeys, 28 days apart, produced lens subluxation in 100% of the treated eyes *[see Nonclinical Toxicology]*.

5.4 Retinal Breaks

In the controlled trials, the incidence of retinal detachment was 0.9% in the JETREA group and 1.6% in the vehicle group, while the incidence of retinal tear (without detachment) was 1.1% in the JETREA group and 2.7% in the vehicle group. Most of these events occurred during or after vitrectomy in both groups. The incidence of retinal detachment that occurred pre-vitrectomy was 0.4% in the JETREA group and none in the vehicle group, while the incidence of retinal tear (without detachment) that occurred pre-vitrectomy was none in the JETREA group and 0.5% in the vehicle group.

5.5 Dyschromatopsia

Dyschromatopsia (generally described as yellowish vision) was reported in 2% of all patients injected with JETREA. In approximately half of these dyschromatopsia cases there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

6 ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in the labeling:

- Decreased Vision *[see Warnings and Precautions]*
- Intravitreal Injection Procedure Associated Effects *[see Warnings and Precautions and Dosage and Administration]*
- Potential for Lens Subluxation *[see Warnings and Precautions]*
- Retinal Breaks *[see Warnings and Precautions and Dosage and Administration]*

6.1 Clinical Trials Experience

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

Approximately 800 patients have been treated with an intravitreal injection of JETREA. Of these, 465 patients received an intravitreal injection of ocriplasmin 0.125 mg (187 patients received vehicle) in the 2 vehicle-controlled studies (Study 1 and Study 2).

The most common adverse reactions (incidence 5% - 20% listed in descending order of frequency) in the vehicle-controlled clinical studies were: vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment, and retinal edema.

Less common adverse reactions observed in the studies at a frequency of 2% - < 5% in patients treated with JETREA included macular edema, increased intraocular pressure, anterior chamber cell, photophobia, vitreous detachment, ocular discomfort, iritis, cataract, dry eye, metamorphopsia, conjunctival hyperemia, and retinal degeneration.

Dyschromatopsia was reported in 2% of patients injected with JETREA, with the majority of cases reported from two uncontrolled clinical studies. In approximately half of these dyschromatopsia cases there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenicity for this product has not been evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Teratogenic Effects

Pregnancy Category C. Animal reproduction studies have not been conducted with ocriplasmin. There are no adequate and well-controlled studies of ocriplasmin in pregnant women. It is not known whether ocriplasmin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The systemic exposure to ocriplasmin is expected to be low after intravitreal injection of a single 0.125 mg dose. Assuming 100% systemic absorption (and a plasma volume of 2700 mL), the estimated plasma concentration is 46 ng/mL. JETREA should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether ocriplasmin is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when JETREA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, 384 and 145 patients were ≥ 65 years and of these 192 and 73 patients were ≥ 75 years in the JETREA and vehicle groups respectively. No significant differences in efficacy or safety were seen with increasing age in these studies.

10 OVERDOSAGE

The clinical data on the effects of JETREA overdose are limited. One case of accidental overdose of 0.250 mg ocriplasmin (twice the recommended dose) was reported to be associated with inflammation and a decrease in visual acuity.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity or reproductive and developmental toxicity studies were conducted with ocriplasmin.

13.2 Animal Toxicology and/or Pharmacology

The ocular toxicity of ocriplasmin after a single intravitreal dose has been evaluated in rabbits, monkeys and minipigs. Ocriplasmin induced an inflammatory response and transient ERG changes in rabbits and monkeys, which tended to resolve over time. Lens subluxation was observed in the 3 species at ocriplasmin concentrations in the vitreous at or above 41 mcg/mL, a concentration 1.4-fold above the intended clinical concentration in the vitreous of 29 mcg/mL. Intraocular hemorrhage was observed in rabbits and monkeys.

A second intravitreal administration of ocriplasmin (28 days apart) in monkeys at doses of 75 mcg/eye (41 mcg/mL vitreous) or 125 mcg/eye (68 mcg/mL vitreous) was associated with lens subluxation in all ocriplasmin treated eyes. Sustained increases in IOP occurred in two animals with lens subluxation. Microscopic findings in the eye included vitreous liquefaction, degeneration/disruption of the hyaloideo-capsular ligament (with loss of ciliary zonular fibers), lens degeneration, mononuclear cell infiltration of the vitreous, and vacuolation of the retinal inner nuclear cell layer. These doses are 1.4-fold and 2.3-fold the intended clinical concentration in the vitreous of 29 mcg/mL, respectively.

14 CLINICAL STUDIES

The efficacy and safety of JETREA was demonstrated in two multicenter, randomized, double masked, vehicle-controlled, 6 month studies in patients with symptomatic vitreomacular adhesion (VMA). A total of 652 patients (JETREA 464, vehicle 188) were randomized in these 2 studies. Randomization was 2:1 (JETREA:vehicle) in Study 1 and 3:1 in Study 2.

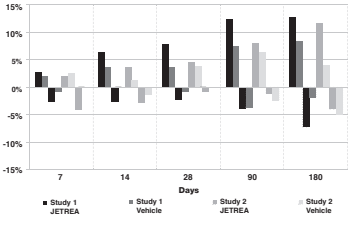
Patients were treated with a single injection of JETREA or vehicle. In both of the studies, the proportion of patients who achieved VMA resolution at Day 28 (i.e., achieved success on the primary endpoint) was significantly higher in the ocriplasmin group compared with the vehicle group through Month 6.

The number of patients with at least 3 lines increase in visual acuity was numerically higher in the ocriplasmin group compared to vehicle in both trials, however, the number of patients with at least a 3 lines decrease in visual acuity was also higher in the ocriplasmin group in one of the studies (Table 1 and Figure 1).

Table 1: Categorical Change from Baseline in BCVA at Month 6, Irrespective of Vitrectomy (Study 1 and Study 2)

Study 1			
	JETREA	Vehicle	Difference
	N=219	N=107	(95% CI)
≥ 3 line Improvement in BCVA			
Month 6	28 (12.8%)	9 (8.4%)	4.4 (-2.5, 11.2)
> 3 line Worsening in BCVA			
Month 6	16 (7.3%)	2 (1.9%)	5.4 (1.1, 9.7)
Study 2			
	JETREA	Vehicle	Difference
	N=245	N=81	(95% CI)
≥ 3 line Improvement in BCVA			
Month 6	29 (11.8%)	3 (3.8%)	8.1 (2.3, 13.9)
> 3 line Worsening in BCVA			
Month 6	10 (4.1%)	4 (5.0%)	-0.9 (-6.3, 4.5)

Figure 1: Percentage of Patients with Gain or Loss of ≥ 3 Lines of BCVA at Protocol-Specified Visits



16 HOW SUPPLIED/STORAGE AND HANDLING

Each vial of JETREA contains 0.5 mg ocriplasmin in 0.2 mL citric-buffered solution (2.5 mg/mL). JETREA is supplied in a 2 mL glass vial with a latex free rubber stopper. Vials are for single use only.

Storage

Store frozen at or below -4˚F (-20˚C). Protect the vials from light by storing in the original package until time of use.

17 PATIENT COUNSELING INFORMATION

In the days following JETREA administration, patients are at risk of developing intraocular inflammation/ infection. Advise patients to seek immediate care from an ophthalmologist if the eye becomes red, sensitive to light, painful, or develops a change in vision *[see Warnings and Precautions]*.

Patients may experience temporary visual impairment after receiving an intravitreal injection of JETREA *[see Warnings and Precautions]*. Advise patients to not drive or operate heavy machinery until this visual impairment has resolved. If visual impairment persists or decreases further, advise patients to seek care from an ophthalmologist.

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retinal video recording instead," he continues. "This approach is quicker and easier to learn than traditional retinal photography, and it provides a greater field of view than three-field retinal photography—a view that simulates what is seen with a slit-lamp examination. And because this technique is easy to learn with minimal training, both medical and non-medical personnel can screen and monitor for diabetic retinopathy in the community, particularly in remote areas and developing countries."

Dr. Ting's group uses the EyeScan instrument from Ophthalmic Imaging Systems (Sacramento, Calif.) to record the videos. He says the idea for this approach to diabetic retinopathy screening came about because of the increasing need for screening that was evident in Australia. "Professor Yogesan Kanagasingam at Lions Eye Institute in Perth, Western Australia, developed the EyeScan instrument in 2009," he explains. "He incorporated the retinal video recording function into the camera so that he could evaluate the effectiveness and user-friendliness of retinal video recording as a way to screen for diabetic retinopathy."

Photos vs. Video

Dr. Ting's group has published two studies of the new technique. The first compared their method of retinal video screening, using the EyeScan device, to the more traditional approach. Fundus images of 100 patients were captured by both photography and video; the results were interpreted by two ophthalmologists. The patients were also examined using slit-lamp biomicroscopy.

Compared with slit-lamp examination results, the sensitivity and specificity of video recording for detecting the presence of any diabetic retinopathy were 93.8 percent and 99.2 percent respectively for ophthalmologist #1, and 93.3 percent and 95.2 percent for ophthalmologist #2. By comparison, the sensitivity and specificity of traditional retinal photography were 91.8 percent and 98.4 percent respectively for ophthalmologist #1, and 92.1 percent and 96.8 percent for ophthalmologist #2. Both imaging methods had 100-percent sensitivity and specificity in detecting more severe, sight-threatening diabetic retinopathy.

"[Video technology] clearly has the potential to be used by specialists as an in-office screening tool to diagnose and monitor patients with diabetic retinopathy."
— Daniel Ting, MBBS

Dr. Ting's group then conducted a second study to determine the optimal compression of the video recordings to reduce the size of the files. "For this study, the retinal video recording was performed by a senior ophthalmology resident medical officer who received a full day of training in using the device," he says. "All retinal video recordings commenced at the optic disc and proceeded to the macula and temporal regions. In order to obtain continuity of retinal information between the regions, the retinal camera was moved at a consistent pace from left to right for the right eye (optic disc, macula and temporal retina) for at least five seconds, and vice versa for the left. This screening process takes about 15 to 20 seconds per eye. For the purposes of our study, we downloaded and compressed the file size of the retinal videos. They were then interpreted by the other two retinal specialists in our center."

Thirty-six retinal videos were compressed from 1 GB to 100 MB, 30 MB, 20 MB and 5 MB; the videos were interpreted by an ophthalmologist and a resident. Sensitivity and specificity were compared to the uncompressed videos. The sensitivity and specificity were greater than 90 percent for all compressed levels except 5 MB, where it dropped to 70.6 percent sensitivity and 94.7 specificity for the doctor and 80 percent and 72.2 percent for the resident.

"Because compressing the files doesn't undercut their usefulness—and the video can be taken by non-medical personnel—this approach can be easily used for diabetic retinopathy screening in routine, mobile and tele-ophthalmology settings," Dr. Ting points out. (He adds that compression of the files might not be necessary in routine screening.)

An Approach with Potential

Although the EyeScan device is currently used in clinics in many countries around the world, Dr. Ting says this kind of screening could be done with other video cameras if their function is similar to the EyeScan. "When we did our first study, EyeScan was one of the first retinal cameras to have this capability," he explains. "That gave us the opportunity to be one of the first groups to describe this novel technique.

"The EyeScan was invented with the goal of increasing the diabetic retinopathy screening rate in the community by making it more affordable," he adds." For that reason, it's currently mainly used in primary-care settings. But it clearly has the potential to be used by specialists as an in-office screening tool to diagnose and monitor patients with diabetic retinopathy." REVIEW

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Panel 1:

LASER AND CATARACT SURGERY WITH TORIC AND MULTIFOCAL IOLS

-Technology and market overview
-Peer review literature
-Practice Integration

Panel 2:

CASE STUDY PRESENTATIONS

-Phaco post laser assisted cataract surgery
-Monofocal IOL implantation
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Staying Afloat in the Perfect Storm

Christopher Kent, Senior Editor

With more patients, government monitoring and shrinking reimbursements, surgeons are looking for options. Here's help.

Surgeons today are faced with a confluence of daunting circumstances: the prospect of a forthcoming major increase in patient load, increased government monitoring and decreasing reimbursements (combined with a slow upward creep in the cost of salaries and supplies). Given that these factors are beyond most doctors' ability to control, the best option—short of drastic changes in practice model or career path—is to increase efficiency and look for ways to make better use of available resources.

Here, three surgeons and a practice administrator, all known for their effective use of limited resources both in the office and in the operating room, offer a host of practical suggestions for not only surviving, but thriving in the midst of challenging times.

Maximizing Clinic Efficiency

Nothing undermines efficiency—and increases costs—like bottlenecks in the office. (This is especially true given the increasing paperwork demanded by insurance companies and government regulations.) These strategies can help minimize day-to-day problems and delays:

• ***Make it easy for doctors and staff to track office activity.*** "Knowing what's happening throughout the practice at any given moment is very helpful," notes Mark M. Prussian, MBA, who has served as administrator of two large ophthalmology practices since 1989. "It helps us juggle the workflow; it tells me who's available to handle pharmacy calls, and so forth. If our office had no ceiling, I could look down from above and see what was happening in every exam room, but our EHR system does this for us; it's part of the patient-flow management software. We can see onscreen where the patients are, where the doctors are, where staff members are, what's happening in each exam room and how long someone has been in the exam room with a given patient. You can see that one patient is almost ready for the doctor; another is having a laser treatment with the doctor, and they'll be done in two minutes; and so forth.

"To make the most of this, we've placed computers in as many locations as possible, including tech and nurse stations, so everyone has access to this information," he says. "Of course, you have to log in for HIPAA compliance, but once you do, that window stays open in the background. So, the first thing you see is what's happening in the clinic at that moment. I really think this is one of the best benefits of

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R. Bruce Wallace III, MD, FACS

One way to increase efficiency in the OR is to prepare sterile peel-pack kits ahead of time containing the instruments you'll need if an unexpected situation arises, such as tools for performing limbal relaxing incisions (above) or vitrectomy (right).

our EHR system. It helps us make the most of our resources."

• ***Delegate to technicians.*** "I'm a big fan of technicians, both in the clinic and in surgery," says R. Bruce Wallace III, MD, FACS, founder and medical director of Wallace Eye Surgery in Alexandria, La., and clinical professor of ophthalmology at Louisiana State University School of Medicine in New Orleans. "Our technicians are trained on the job to have multiple skills. They do refractions and they understand how to use the slit lamp, even though they're not qualified to do the examination. It streamlines things if I walk into the exam room and everything I need is there on the chart, except the slit lamp exam and retinal exam.

"Furthermore," he continues, "most of our technicians are proficient at scrubbing in for surgery. They're multitalented, and they understand the big picture—not just what's going on in the clinic, but what's happening in the OR. I think that helps them counsel patients better. Being able to have our technicians handle so much is a plus for us."

• ***Be proactive about non-generic prescriptions.*** "Pharmacists and patients seem to be resisting 'Do not substitute for generic' orders more frequently than in the past," notes Mr. Prussian. "They call us and say, 'Are you sure? This medicine is so similar to that one … ' Of course, our doctors only prescribe patent medications if they have a good reason. If the ordering doctor is available at the time the call comes in, he or she may get on the phone and lecture the pharmacist about the difference between the patent medication and the generic. If the doctor isn't available, we may just go into the e-prescribing software and deny the request for a generic.

"Because this has become more of an issue, we're planning to try printing a brochure that we can hand out, explaining why generics are not always as good as patent medications," he says. "We'll also add the explanation to our website, do a Facebook post about it and put it in our blog and our e-newsletter. Hopefully, by tackling the issue before patients take a prescription to the pharmacist, we'll reduce patient unhappiness and be fielding fewer of those time-consuming phone calls."

• ***Keep trying new things.*** "Trying new things is part of our office culture," adds Mr. Prussian. "That includes frequently rearranging the office layout to see if we can improve it. For example, we generally start our in-office care with an autorefraction, so we keep tweaking the location of those instruments to see what works best for patient flow and is easiest for patients. It's one way we challenge ourselves: What can we do better this week?"

Keeping Patients Coming In

To manage this, a practice must keep current patients' experience positive, do everything possible to prevent missed appointments, and be effective at attracting new patients.

• ***Use the computer to customize paperwork.*** "We do this using a Microsoft Word merge program," explains Larry E. Patterson, MD, medical director and surgeon at Eye Centers of Tennessee. "Our staff type in the patient's name, age, allergies, which eye we're operating on, type of surgical procedure and surgical

date and time; the computer prints out 19 pages of fully customized paperwork, both for the patient and the surgery center, including consent forms and patient instructions. We've all had the experience of going to the doctor and receiving instructions that are a copy of a copy of a copy. The paper looks old and faded. Here, everyone gets a newly printed, customized bunch of paperwork. It's efficient and it makes our practice look good."

Larry E. Patterson, MD

Time and resources are conserved if cataract patients stay on a single stretcher throughout the procedure. Monitoring equipment can be attached to the stretcher so it travels with the patient.

• ***Pre-appoint all patients before they leave the practice.*** "Doing this ensures that they have their next appointment set up, even if the appointment is a year later," says Mr. Prussian. "Patients can easily forget to schedule later on, turning a one-year period into 18 or 24 months. Having the appointment already in the system allows us to remind them at the appropriate time. Of course, we will let people skip this if they insist on it."

• ***Use your EMR system to alert you when a patient has not come in within an appropriate interval.*** "Even if we give patients an appointment and remind them, it doesn't mean they'll show up," notes Mr. Prussian. "So, for example, we'll have the computer generate a list of people with a glaucoma diagnosis who have not been in in the past year. Then, when the staff has a lighter workload on a day most of our doctors are in surgery, one person will call the patients on the list and say, 'I'm calling on behalf of Dr. So-and-so; he's noted that you missed your six-month glaucoma check. He has an opening next Thursday at 3:00; can we schedule that now?' Overwhelmingly, patients agree to come back in."

• ***Consider promoting your services and special events on Facebook.*** "I continue to find that regardless of what I try as a way to advertise our LASIK services, Facebook and Google AdWords outperform any other medium that I've tried buying over the past couple of years," says Mr. Prussian. "Today it's challenging to reach potential patients who don't have a landline telephone, read newspapers or even watch live television any more. Facebook is one good way to reach them. You put up a witty posting and pay Facebook to find your demographic, such as people who 'like' us on Facebook, or have certain interests, or live in a given area. It's pretty intuitive. Even better, it's very easy to track the results.

"For example, I recently decided to advertise a LASIK seminar to a market I had never previously targeted," he continues. "I hadn't done much with country radio, so I thought it might be a way to reach new people with our message. We spent $3,000 on a one-month country radio campaign; at the same time, we spent $350 on Facebook ads, which took you to a registration page. About 80 percent of the people who showed up registered online through the Facebook ad; only about 20 percent heard about it on the radio station. The Facebook ad cost $350 and produced four times the response of the $3,000 radio ad."

• ***Simplify your advertising.*** Mr. Prussian notes that a straightforward, simple message is more likely to get a response. "The word LASIK has become sort of generic, like the word Kleenex is to facial tissue," he points out. "So, our advertisements generally just mention LASIK, because I believe the public equates that with improving your vision. When the patient is in the office, we do the examination and explain that he has cataracts or glaucoma or would be a great LASIK patient. But our message is targeted to say LASIK. It's simple and effective."

• ***If you have an optical shop, have the patient pick up his glasses prescription there***. Many surgeons generate additional income by having an in-office optical shop. In that situation, it's helpful to encourage patients to at least spend a few moments in that part of the practice so they're aware of the option of purchasing their glasses without having to make an extra trip to another location. One way to accomplish that is to have patients' lens prescriptions print out in the optical shop for them to pick up.

"This is easy to arrange if you're using electronic medical records," says Mr. Prussian. "If the patient picks up the prescription in the optical shop, he's more likely to purchase the glasses from you. We also have the doctor check any appropriate boxes for items such as UV protection or anti-reflective coating that he believes are medically appropriate; the optician then explains the reasons for those recommendations to the patient."

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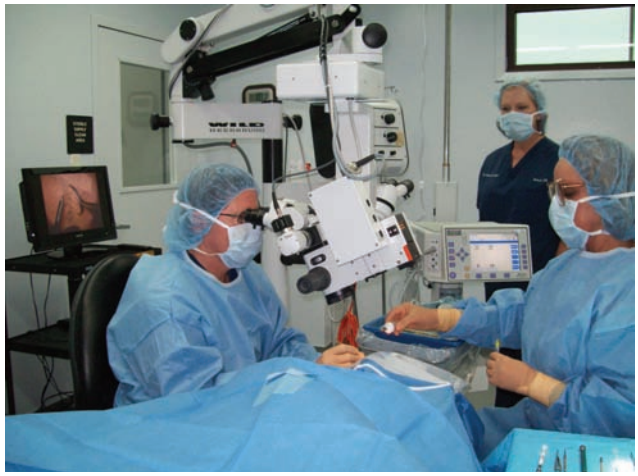

Richard J. Ruckman, MD

Many surgeons schedule all left eyes together and right eyes together to eliminate rearranging equipment. However, even uder the best of circumstances, that schedule may be disrupted. This makes it important to set up the OR so that all relevant equipment can be easily switched from a left eye format to a right eye format, and vice versa, as in the operating room shown above.

Managing Costs

This can be a challenge, especially if you don't want to undermine the quality of patient care.

• ***If your EHR system handles many of your mailings, consider not using a postage meter.*** "When the volume of mailing you're managing in-office drops below a certain level, it's more cost-effective not to use a postage meter," says Mr. Prussian. "Instead, it makes sense to have a trustworthy staff member simply buy stamps at face value in the post office and keep them in a safe place. Ten years ago we sent out several thousand pieces of mail a week. Now our computer system sends out patient statements, so we only send out 200 to 300 pieces of mail each week. In this situation I've found that it's a better value not to be locked into a postage meter contract and have all of the expenses associated with that."

• ***Don't focus solely on the cost of supplies.*** "Surgeons often ask about reducing the cost of surgical supplies," notes Richard J. Ruckman, MD, president and medical director of The Center for Sight in Lufkin, Texas. "However, supplies are the smallest part of the cost of doing business in the ASC. Salaries are the biggest cost, typically 43 percent of the cost of doing business; overhead is second, typically 33 percent; and supplies are third, at about 23 percent. Sometimes someone worrying about the cost of a particular supply overlooks how long it takes to do the surgery, or how many people it takes. So it's important to remember that there's more than one way to reduce costs."

• ***Don't scrimp on autoclaves***. "Make sure you have adequate autoclaves to handle your volume," says Dr. Ruckman. "This is not the place to try to save money. Any problems that arise as a result of incomplete disinfection could cause major time and energy drains, in addition to putting patients at risk."

Surgery: Planning Ahead

"A good way to define efficiency is: maintaining or developing the highest quality and taking the shortest amount of time—without accepting unnecessary risks," notes Dr. Patterson. "In practical terms, to be efficient in the OR, you need to reduce all aspects of the operation to their most essential elements. If you have a 20-step procedure and you can reduce it to a 10-step procedure, you're not only allowing things to happen more quickly and more smoothly, you've just eliminated 10 things that can go wrong. So it's worth stepping back from time to time, looking carefully at the process, and asking yourself: Is there a reason we do each of these steps?

"Generally, I think a cataract surgeon with a single OR should be able to do about four cases an hour," he continues. "If you have two operating rooms, you should be able to manage five or six cases an hour, going back and forth from room to room. I often talk to surgeons who have two rooms and are only doing three cases an hour. That's a huge waste if they're routine cataract cases. In fact, if you're doing less than that—two cases an hour—then you'd probably be better off financially just staying in the office and seeing patients. That's not a business model that will work."

Doing a number of things ahead of time will help make surgery go as smoothly as possible:

• ***Hire an experienced surgical coordinator.*** "It's important to have one or two people, depending on how big your staff is, to focus on managing all the issues surrounding surgery," says Dr. Patterson. "Your surgical coordinator can do preop testing and consultation, insurance precerts, scheduling, assembling the IOL

power calculations, doing phone calls with the patients preop and postop and coordinating with your surgery center. Depending on your setup, the coordinator may also be able to go into the OR and help with turnover. This person's job is to make sure everything goes as smoothly as possible the day of surgery, so there aren't any surprises. This can have a real impact on your efficiency."

• ***Prepare instrument packs ahead of time.*** "It's efficient and cost-effective to prepare sterile peel-pack kits containing the instruments you need for a particular surgical situation," says Dr. Wallace. "We create a cataract pack; we also have kits for special circumstances such as when a patient needs an LRI, or I need to perform a vitrectomy. Because we have the kits, we don't have to assemble all these separate tools and sutures. Everything is ready to go whenever it's needed."

• ***Have a compounding pharmacy combine your preop drops.*** "We have our dilation drops, a nonsteroidal and an antibiotic all compounded together," says Dr. Patterson. "There are places that will do this for you pretty inexpensively. Once this is done, you just have to put in a few drops; you don't have to go back to the patient over and over again. Of course, we still keep individual drops such as the dilating drops available in case we need more of them."

• ***Aim to schedule left or right eyes together.*** "Since most of us operate temporally, I think it's important to try to do all your right eyes together and left eyes together so you don't have to change the OR setup back and forth," says Dr. Patterson. "That's something you can do ahead of time that will make your day run smoother. And, if you have two ORs, you can set up one OR for right eyes and the other for left eyes."

• ***Set up the OR so you can easily switch from left to right eye with minimal rearrangement.*** "Even if you try to group your eyes so you do all left or right eyes at once, things often get out of order," notes Dr. Ruckman. "We arrange our ORs so that we can switch from a left eye to a right eye with minimal work. *(See example, facing page.)* The less you have to change, the smoother your flow will be throughout the day."

• ***Have a monitor in the OR that allows others to view the surgery.*** "It's important to have a monitor in the OR so the anesthesia professional can see how the surgery is going," says Dr. Wallace. "He or she will know if there's any unusual eye movement,

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Larry E. Patterson, MD

At the beginning of the surgical day it helps to have the first few patients arrive in rapid succession. At this point, postop staff are available to help prepare patients, and the day's schedule gets off to a solid start.

and be able to communicate effectively with the surgeon in regards to what medications to give at what time."

Dr. Ruckman adds that the monitor has other benefits as well. "Because my assistant is not looking through the microscope, she may not know exactly where I am in the procedure," he says. "She can actually follow the procedure more easily on the monitor and have my next instrument available immediately. The circulator is constantly aware of where we are in the procedure and can better anticipate a need for extra instruments or supplies. The monitor also lets our transporters know when to be in position to move the patient from the room."

• ***If possible, arrange your OR so you can see the preop and postop areas.*** "We have two identical operating rooms, and everything is compact enough that I can stand in one position and see everything going on," says Dr. Ruckman. "I think that adds to efficiency, because I don't have to run all over the building to know what's happening in the pre- and postop areas. Obviously, not every building design will allow that, but it's an advantage if you can arrange it."

• ***Schedule more complex cases later in the day.*** "Obviously, more complex cases are likely to require more time and can be more disruptive to the schedule," notes Dr. Ruckman. "Scheduling them later in the day minimizes the disruption and gives us more time to focus on the patient. It also keeps the other patients and their families calmer; they get more anxious when their surgeries are delayed."

• ***Save detailed postop instructions for post-surgery.*** "We provide written preop instructions and a review of postop care in the clinic prior to surgery," says Dr. Ruckman. "However, we've found that it's much more efficient to provide the detailed postop instructions only in the recovery area; otherwise we end up providing them twice."

• ***Don't assume all OR personnel have to be RNs.*** "I've seen some places where everyone in the OR other than the surgeon is a registered nurse," says Dr. Patterson. "That's overkill. Nurses have to do some things, including putting in eye drops and giving medications. But non-nursing personal can help get people on and off the stretcher, adjust the patient's head, change sheets, get the patient warm blankets, and so forth."

• ***If possible, share staff between clinic and ASC.*** "Our surgery center is part of our clinic," says Dr. Ruckman. "We have a full-time RN director in the ASC, but the clinic and ASC share staff. As a result, the staff in the surgery center know the patients because they've been working with them. That helps things go smoothly."

On the Day of Surgery

These strategies will help get things off to a good start:

• ***Be on time.*** "This is an important point for doctors, because staff are usually pretty good at this," notes Dr. Patterson. "The surgeon may feel it's his prerogative to be a little late, but that will undercut your efficiency and discourage your staff."

In fact, Dr. Ruckman sees an advantage to getting there ahead of time. "Arriving a few minutes early allows me to check both operating rooms to see that the microscopes are working properly and everything is set up correctly," he notes. "This saves time by preventing problems later."

• ***Prepare a "summary sheet" at the beginning of the surgical day.*** "Once we know what the schedule is, my nurse prepares a sheet showing what we anticipate the order of cases will be," explains Dr. Ruckman. "I then add the proposed lens that I want to use for each case, although I

Larry E. Patterson, MD

Having a staff member adjust the patient's head position and the height of the table in the preop area saves time in the OR.

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For patients with decreased tear production presumed to be due to ocular inflammation associated with Chronic Dry Eye

RESTASIS® MAKES MORE OF THEIR OWN REAL TEARS POSSIBLE

Prescribe RESTASIS® for your appropriate moderate and severe Dry Eye patients and increase their own real tear production over time with continued use

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Indication and Usage

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

Important Safety Information

Contraindications

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

Warnings and Precautions

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, individuals prescribed RESTASIS® should not touch the vial tip to their eye or other surfaces.

Use With Contact Lenses: RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion.

Adverse Reactions

In clinical trials, the most common adverse reaction following the use of RESTASIS® was ocular burning (upon instillation)—17%. Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Please see Brief Summary of the full Prescribing Information on adjacent page.

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RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05%
BRIEF SUMMARY—PLEASE SEE THE RESTASIS® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.
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WARNINGS AND PRECAUTIONS
Potential for Eye Injury and Contamination
To avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces.
Use with Contact Lenses
RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.
ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In clinical trials, the most common adverse reaction following the use of **RESTASIS®** was ocular burning (17%).
Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).
Post-marketing Experience
The following adverse reactions have been identified during post approval use of **RESTASIS®**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the vial tip touching the eye during administration).
USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects: Pregnancy Category C
Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 5,000 and 32,000 times greater (normalized to body surface area), respectively, than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater (normalized to body surface area), respectively, than the daily human dose.
Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 7,000 times greater than the daily human topical dose (0.001 mg/kg/day) normalized to body surface area assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily human dose).
There are no adequate and well-controlled studies of **RESTASIS®** in pregnant women. **RESTASIS®** should be administered to a pregnant woman only if clearly needed.
Nursing Mothers
Cyclosporine is known to be excreted in human milk following systemic administration, but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of **RESTASIS®** ophthalmic emulsion, caution should be exercised when **RESTASIS®** is administered to a nursing woman.
Pediatric Use
The safety and efficacy of **RESTASIS®** ophthalmic emulsion have not been established in pediatric patients below the age of 16.
Geriatric Use
No overall difference in safety or effectiveness has been observed between elderly and younger patients.
NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.
In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 80 times greater (normalized to body surface area) than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.
Mutagenesis: Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).
Impairment of Fertility: No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.
PATIENT COUNSELING INFORMATION
Handling the Container
Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion. To avoid the potential for injury to the eye, advise patients to not touch the vial tip to their eye.
Use with Contact Lenses
RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.
Administration
Advise patients that the emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.
Rx Only

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don't list the lens power; we always go back to the original document to identify the power in the OR immediately prior to the procedure so there's no room for transcription errors.

"The sheet also includes other elements that are relevant to the case," he continues. "First of all, is it a complex surgery? Listing that helps ensure that the billing department will bill it as a complex case. Am I going to use special instruments? Will there be a pterygium? Will I need Trypan blue? We do our best to anticipate this so the staff is ready and expecting it. I also make notes about anesthesia; whether I think the patient is anxious and needs more sedation, or how the patient reacted during the first case and how this might affect the second eye. The list follows the nurses and technicians from room to room, but it's also posted in all the rooms and preop areas, on a clipboard where only staff can see it, so everybody knows what's happening when."

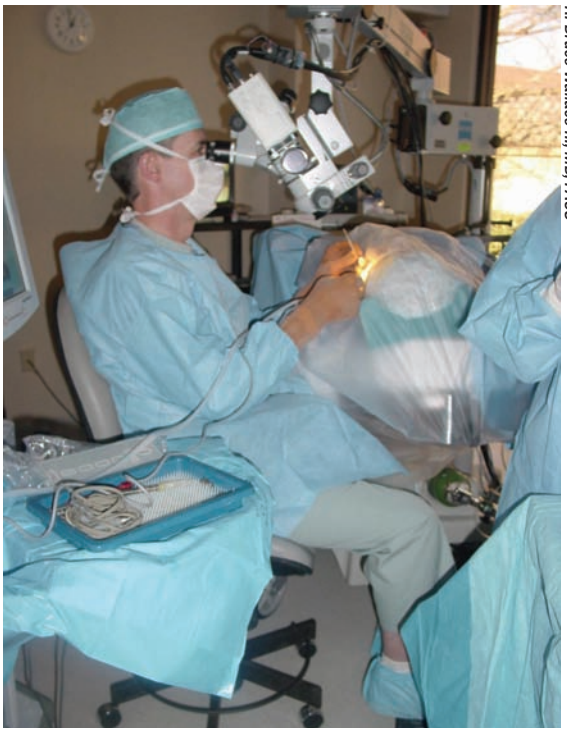
• ***Have the first three patients arrive at about the same time.*** "At the beginning of the day we have the most staff available to help in the preop area," explains Dr. Ruckman. "The RN who usually stays in the postop area can help in the preop area at that time, and it creates kind of a wave at the beginning. That makes good use of our resources and gets us off to a good, consistent start. We do stagger the patient arrivals a little; one arrives at 7:00, one at 7:10, one at 7:20. But in effect, we have three patients in preop at the same time."

• ***Keep the patient on one stretcher from start to finish.*** "Once the patient comes in he's put on a stretcher," says Dr. Ruckman. "We hook up the blood pressure and vital sign monitors in the preop area. The monitor stays on the stretcher, so once the patient is hooked up, we don't have to unhook anything until the patient is in recovery. We also use leads on each wrist to monitor the heart rate, which saves

us from having to expose the chest to put on chest leads."

"Moving the patient as little as possible saves time and reduces back strain," notes Dr. Patterson. "When it's time for surgery, we just recline the stretcher, go straight into surgery, do the surgery with the patient on the stretcher and then move the stretcher into postop. I've seen lots of surgery centers where they have a standard OR table and they have to move the patient from the stretcher to the table and back to the stretcher. That's not necessary."

• ***Adjust the patient in the preop area.*** Adjust the head, the positioning and the height of the table before you go into the OR," suggests Dr. Patterson. "The nurses or their assistants can do this."



R. Bruce Wallace III, MD, FACS

Eliminating surgeon back strain prevents a host of problems and slowdowns during surgery. When operating temporally, tilting the microscope 45 degrees toward the surgeon allows the surgeon to sit back in the chair while working, dramatically reducing back strain. A bolster can also be placed under the patient to tilt the patient's body.

During the Surgery

To keep things moving smoothly and avoid unnecessary delays:

• ***Don't wait until everything is prepared to bring in the patient.*** "The room doesn't have to be completely set up when the next patient is brought in," says Dr. Patterson. "I've seen the old hospital way of doing things; they wouldn't let you bring the patient in until all of the equipment was set up and everything was ready to go. That's silly. We'll often bring a patient into the room while they're still opening things up on the back table and tuning the phaco machine. If we get ready to operate and everything still isn't finished being set up, we just wait a few seconds or a minute and let them finish. As a rule, we've got this down so that everything is ready when we need it."

• ***Have staff prep the patient.*** "One person in our OR preps the eye; then the technician who's helping in surgery drapes the lid and lashes," says Dr. Wallace. "When I come in, the eye is basically ready to go for surgery. Our technicians and RNs handle all of the preparation without anybody else needing to be present in the room."

• ***Emphasize constant communication.*** "Communication should occur as the patient is transferred from one area to the next, so the RN is aware of what is going on," says Dr. Ruckman. "Furthermore, communication has to happen both from the top down and the bottom up. Everybody needs to be aware of what's going on with each patient, and not being afraid to point out or question anything. Each person is responsible for his or her own tasks, but everyone should also be aware of what everybody else is doing."

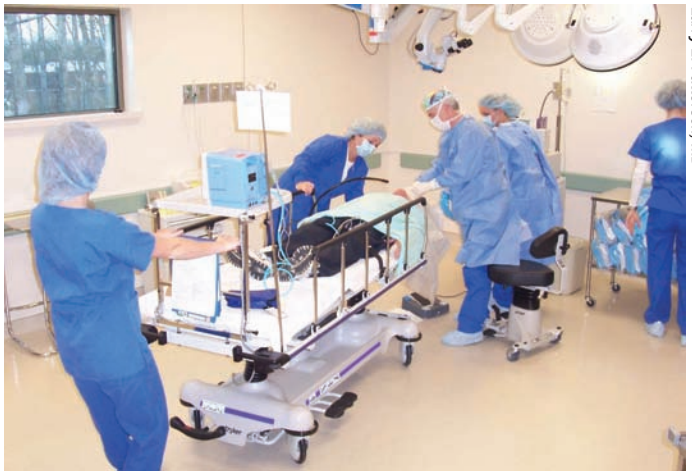
• ***Don't skip the pre-surgery "time out" in the name of efficiency.*** "This is one government regulation that I've found to be good," says Dr. Ruckman. "Before you start the case, you're supposed to take a time out and get everyone to focus on the patient for just a minute. Everybody stops and agrees that we have the right patient, the right diagnosis, the correct eye, and allergies are identified. Everybody verbally states that they agree, and then we proceed with the surgery.

"It's been argued that this is a waste of time, but I don't think so," he says. "I call for the time out while I'm looking at the record, I confirm the IOL, and I call out the information. The CRNA will say, 'I agree'; my RN who is holding the lens says, 'I agree.' It takes about 30 seconds. It confirms that everyone is on the same page and prevents time-consuming errors."

• ***Adjust the microscope so you can sit back in the chair.*** If the surgeon is uncomfortable or in pain, efficiency will suffer. "I'm a big proponent of being careful with surgeon posture," says Dr. Wallace. "I recommend tilting the microscope 45 degrees toward the surgeon; that allows you to sit back in the chair as you work. Some of these cases unexpectedly go on for a fairly long time if you have a complication, and the surgeon doesn't get to stand up and walk around the room and stretch. The surgeon has to stay in that position until the case is finished, which could be an hour or more.

"I've had many doctors come up to me and tell me they were ready to retire as a result of physical injury, until they tried switching to a 45-degree tilt," he adds. "When we were operating superiorly we couldn't do this; but now that we're operating temporally we can tilt the patient's head 45 de-

grees. Jim Gills, director of St. Luke's Cataract & Laser Institute in Florida, uses this technique; he even puts a bolster under the patient's opposite shoulder, so the whole body of the patient is tilted 45 degrees. We do this as well." (For more on this, see Dr. Wallace's article in the *Journal of Cataract and Refractive Surgery*.[1])



Larry E. Patterson, MD

To save time and avoid unnecessary delays, preparations for the next patient can begin even while the current patient's surgery is being completed. In the same spirit, removal of the patient can begin even as the surgeon is peeling the sterile drape from the face (above).

• ***Include potential time-saving surgical techniques in your repertoire.*** "For example," says Dr. Wallace, "when performing cataract surgery I'm sometimes successful with cortical cleaving hydrodissection, described by Howard Fine in 1992. With this technique you try to inject the BSS not just around the nucleus, but the cortex as well; a successful attempt is confirmed by a peripheral fluid wave. When this works, removing the nucleus also removes the cortex, so you can skip the cortical irrigation and aspiration step. I'm not able to make this work 100 percent of the time, but when it does work, it's more efficient."

• ***Be a part of your team.*** "Many surgeons disappear for a few minutes between cases," notes Dr. Patterson. "They may go back and sit in the lounge and wait to be called. That's not efficient, and it doesn't encourage the rest of the surgical team, who continue working to get ready for the next case. The doctor can grab a stretcher and help move the patient, or go out into the preop or postop areas and see what can be done. If the room needs to switch from left eye to right eye, he can move the microscope pedal and phaco pedal. It's a mindset issue. If the doctor is working the whole time, it's not only more efficient but it helps everyone else feel good about working as well. And it's especially important to do this on days when the staff is shorthanded, such as when someone is out sick. It can make a big difference."

• ***Don't deal with other concerns during surgery hours.*** "This relates to the previous point," notes Dr. Patterson. "I've talked to consultants who say that surgeons are notorious for taking phone calls from their stockbrokers, families or friends between cases. They don't keep their minds focused on what's happening in the surgery center. This is discouraging for the staff and a potential time sink, so if you've got a morning blocked off to do surgery, just do surgery. Leave your cellphone in your office or in the locker room. If there's an emergency, people will be able to get hold of you. Let the rest of it go."

• ***Don't wait for the end of the case to begin preparing for the next case.*** "Although we have everything we need for cataract surgery on the mayo stand, which in our case is integrated with the phaco machine, we also have a back table where a staff member opens packages, sets things up and loads the lens," says Dr. Patterson. "We don't wait for the case to be finished before one of the staff begins clearing off the back table. While we're putting the implant in, the back table is being cleared and prepared for the next case. This saves considerable time."

Postop Efficiency

These strategies can help prevent bottlenecks and extra post-visit phone calls:

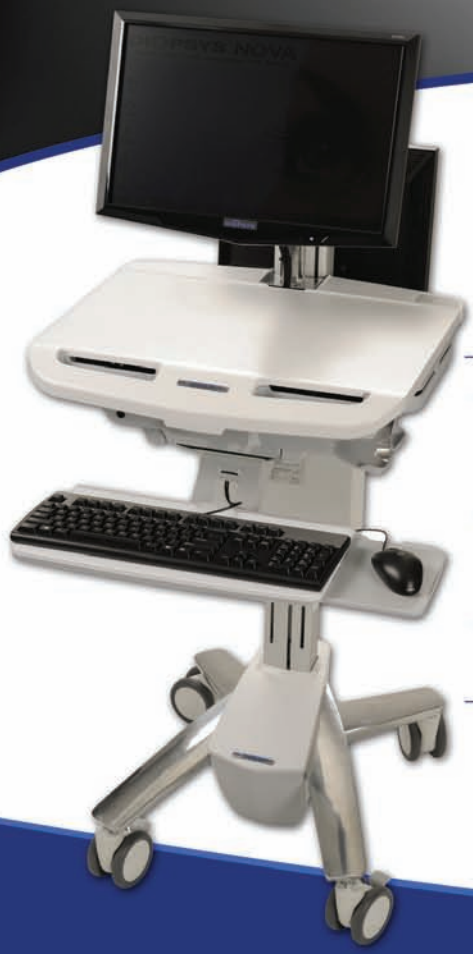
• ***Don't keep patients in postop longer than necessary.*** "We have a very short postop period," notes Dr. Patterson. "It helps that we don't routinely use patient IVs; we just give patients mild oral sedation. Partly for that reason, most of our patients only remain in the postop room for 10 or 15 minutes. If their vitals are normal, they've been able to drink some juice and they feel OK, we put them in a wheelchair and let them go home. This avoids tying up space. Even if space isn't a problem, the more people you have sitting around, the more staff you have to have, watching and tending to them.

"Our ideal is for someone to come in and leave within an hour to an hour and 15 minutes," he adds. "We achieve that most of the time. Not always, but most of the time."

• ***Have printed postop instructions for the patient and family member.*** Since the patient could still be somewhat amnestic, we make sure that all instructions are printed and request that a family member be present at the same time," says Dr. Ruckman. "Everything is printed for the family member as well, which reinforces what to do and what to expect."

When Management Resists

Dr. Ruckman, who along with Drs. Wallace and Patterson teaches the surgical efficiency course at the annual



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Larry E. Patterson, MD

Surgeons often disappear between cases. Instead, the surgeon can help move the patient, reset equipment or assist in the preop or postop areas. This increases efficiency and helps improve staff morale.

American Academy of Ophthalmology meeting, notes that questions from the audience often involve how to overcome a hospital or ASC's inertia. "Doctors," he says, "will report that the OR director tells them, 'We can't do it that way. We never have.'

"A good way to address this," he continues, "is to present that person with benchmark data showing that the surgery and patient flow can be done differently without undercutting quality of care, resulting in improved efficiency and time-savings. Studies conducted by the Accreditation Association for Ambulatory Health Care, for example, show how long a cataract surgery case should take, and how long the patient needs to be in preop and postop, as well as providing details about the reasons for the efficiency. Typically those data are based upon several hundred thousand cases.

"For instance, one study of cataract surgery found that the average facility time—the time from the moment the patient walked into the facility until they left—was 119 minutes," he says. "The average preprocedure time was 83 minutes. Operating time was 15 minutes; discharge time was 21 minutes. This gives you some numbers to work with based on a national standard. So if there's a bottleneck in the facility you're using, you can say, "This is a national comparison; why can't we meet this benchmark?" You're providing concrete evidence that the procedure can be done in less time.

"For example, an OR director might insist that patients get completely undressed for surgery, put on a gown, and stay in recovery for at least two hours," he continues. "But the benchmark data show that patients can remain fully dressed for the surgery, and once they meet discharge criteria they can leave in much less than two hours. It gives you some basis for comparison, and it proves that you can get a patient through a facility in two hours instead of three or four, and still provide quality care.

"Unfortunately," he adds, "there's not a lot of this kind of data out there. The AAAHC data is only available free of charge to those who participated in the study. However, you may be able to buy the study, which might be worthwhile if a facility is causing an unnecessary reduction in your efficiency."

Efficiency in Perspective

"Efficiency is a double-edged sword," notes Dr. Wallace. "Ironically, taking less time to do a procedure can lead to further cuts in reimbursement. But if you want to handle more patients, you have to consider at least some steps to make it possible for those extra patients to be taken care of without working into the night and losing good quality staff because they don't like their hours."

Drs. Wallace and Patterson offer a few closing pieces of advice:

• ***Don't take chances.*** "Efficiency is good for the patient," says Dr. Wallace. "However, we can't throw the baby out with the bath water; we have to produce very good results. So if surgeons feel overwhelmed or out of their comfort zone when trying to be more efficient, they should take it slowly. Improving efficiency shouldn't mean taking chances. The last thing any of us wants is to sacrifice patient visual results."

• ***Don't worry about efficiency until you're really good at what you do.*** "To be efficient, you must first be proficient," notes Dr. Patterson. "You have to be good at what you do, first and foremost. If you're coming straight out of residency, you need to become good at doing the surgery; don't worry about efficiency. Complications are very inefficient! Of course, that's not the main reason to avoid complications, but if you're trying to be more efficient, minimizing complications should be high on your list."

• ***Don't try to increase efficiency by working faster.*** "Efficiency will lead to speed, but speed will not lead to efficiency," Dr. Patterson notes in closing. "Rushing will not help; it will just cause more problems. If you're efficient and you do things properly, surgery will go faster. But simply trying to work faster may backfire." REVIEW

1. Wallace, RB. The 45 degree Tilt: Improvement in surgical ergonomics. J Cataract Refract Surg 1999;25:2:1-3

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*United States Census Bureau, *"2010 Census Briefs – Age and Sex Composition: 2010, Table 2"* (2011).

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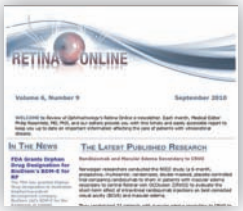

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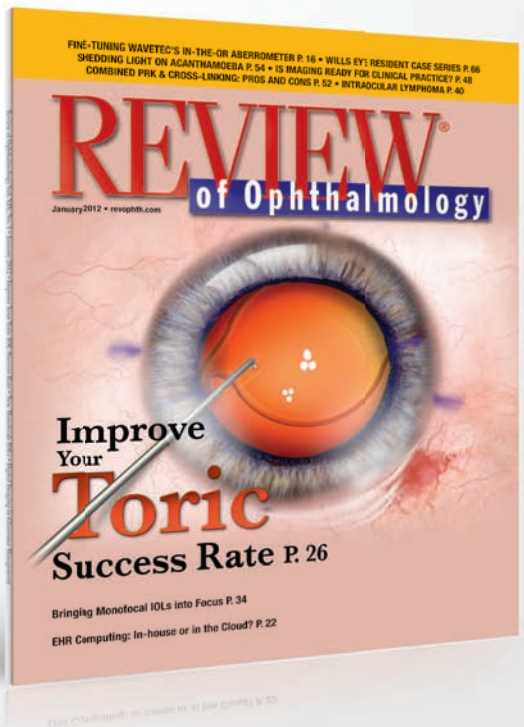

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Mining Your Practice For New Revenue

Walter Bethke, Managing Editor

Your current patients may be interested in premium lenses or cosmetic procedures.

Fear of decreasing reimbursements and uncertainty over the ramifications of the Affordable Care Act have some ophthalmologists thinking of generating alternative streams of fee-for-service revenue in their practices. This can take the form of new procedures, such as cosmetic treatments, or bolstering the offerings the practice already has, such as increasing the percentage of patients who convert to a premium intraocular lens or an upgraded cataract surgery package. Here, ophthalmologists and a practice management expert explain strategies to consider and pitfalls to watch out for when you try to start something new in your practice.

Premium Cataract Surgery

If you already offer premium IOLs, either toric or presbyopia-correcting, one way to increase revenue is to increase your premium IOL conversion rate or offer higher technology options. Here are the issues to consider.

• ***The surgeon must buy into it.*** Cory Pickett, a consultant based at Turner Eye Clinic in Midland, Texas, works with several ophthalmic practices on devising ways to increase their premium surgery revenue. He says that some of the barriers to premium IOL conversion are on the physician's side. "It's pretty simple," he says. "The doctor has to believe that premium IOLs are good for his patients and his practice. If either of those beliefs isn't present, then he will be haphazardly offering these IOLs without any emotion behind it. I've seen doctors who come across as, 'You can have these IOLs if you want,' but there's no focus and, consequently, no increase in conversions. But if the practice makes it a focus and says, 'What steps do we need to take to at least have the opportunity to upgrade?' then that's a big deal." Mr. Pickett says that, by making premium upgrades a priority from the surgeon on down, one practice he works with was able to transition from performing 600 to 700 cataracts a year and converting 10 to 20 of them to toric lenses, to performing 1,000 a year and implanting 300 torics.

• ***Identify and educate the candidates.*** Experts say that, in order to best use your resources and not waste time, you have to make sure the patients you approach with premium lens options can actually use them. "What I teach when visiting practices is, instead of making a recommendation on a lens and then figuring out if the patient is a candidate and can pay for it, do the opposite," says Mr. Pickett. "Figure out what the patient might be a candidate for first, and

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then make a strong recommendation based on that. A classic example is the patient with 2 D of astigmatism who comes in. You make a strong recommendation of a toric IOL for him, but then, a couple of minutes later, you find out that his astigmatism is in his natural lens rather than the cornea, and you have to tell him he isn't a toric candidate after all. Now, you've got to backtrack and have created more confusion for him. When this happens, it's less likely that the patient is going to upgrade to anything at all, and he may just want to get out of there."

Austin, Texas, surgeon Steven Dell agrees. "I think the first step is to identify the correct patients who can have these technologies," he says, "and exclude those who may have disqualifying medical conditions such as severe irregular astigmatism or perhaps loss of contrast sensitivity from glaucoma, diabetic retinopathy or macular degeneration."

If patients are physiologically sound, Dr. Dell has found success using a brief questionnaire to weed out patients who simply aren't interested from those who would like to hear more about their options. "Patients don't always know these technologies exist," Dr. Dell notes. "So they have to be educated about the fact that these are options. One of the ways that we quickly determine whether patients are interested in these technologies or not is to give them a questionnaire that simply asks the distance at which they'd like to see without spectacles after the surgery, if that were an option. One group will say, 'Yes, I'd like to see well at distance and near without glasses,' and another will indicate that they don't really care about that. If a patient doesn't have a goal of getting rid of spectacles, typically we'll check in with him one final time later and ask, 'We wanted to make sure it doesn't really matter to you that you wear spectacles,' and, if he doesn't care, we'll stop the process of educating him about astigmatic and/or presbyopic correction."

All images: Adam Cohen, MD

A professional-looking front desk leaves a positive impression on self-pay patients.

Mr. Pickett says it can pay to have a separate area for educating potential premium IOL patients so they can feel relaxed when reviewing the information. "We created an area we call the Sight Selector that makes use of an iPod, iPad or other media player," he says. "On the device, we can select the conditions the patient might have—such as hyperopia or astigmatism—and it will go through the various lens options and show a consent video. We try to individualize the educational process. Following that, a counselor will meet with the patient and discuss the benefits of specific technologies, but not so much pricing. Then, the doctor will come in and make a strong recommendation, already aware of what the patient's been educated about."

Dr. Dell also thinks electronic media are a big help. "We use educational tools such as products from Eyemaginations, their Echo software in particular," he says. "This allows us to quickly illustrate to the patient what we mean when we talk about presbyopia, and what we really mean when we say 'intermediate vision,' because people may have different ideas about what the intermediate vision distance is."

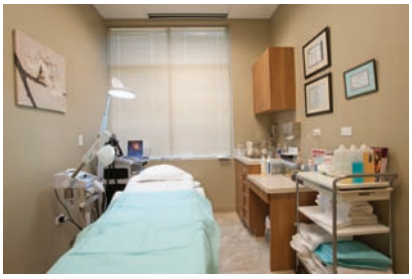
Mr. Pickett says one of the most popular and successful ideas his practice has instituted has been the use of mailers for cataract patients. "When a patient calls for an appointment and has already been diagnosed with a cataract, we send a custom mailer to him showing what the potential options are regarding different lens types and what the fee schedule is," he says. "So, these people actually get an introduction to this information before they even get to the practice. Sometimes, having the fee schedule in it works in our favor because we don't have to discuss the fees too much, and some patients will come in and say, "Yes, I want this particular lens." The mailer also contains a menu that describes the benefit you might get with each lens, with four criteria being distance, near, astigmatism and night vision. This is very easy for the patient to understand. Rather than trying to make him understand the difference between an accommodative lens and a diffractive IOL, this tells him what the potential benefit is to him."

• ***Offer multiple options.*** A big mistake some practices make, the experts say, is only offering two options: a basic surgery and a premium one. If you offer more, the thinking goes, you'll find more patients upgrading in one shape or form. "When it comes to conversion rate, of course everyone wants to convert close to 100 percent," says Mr. Pickett. "Having more options increases this upgradeability. A big patient objection is cost; that's why adding other services is a big deal. We started offering very basic upgrade packages with a simple limbal relaxing incision or the use of extra diagnostic tools to determine which aspheric IOL might be best for a patient who wants one. You build these costs into

a package in a way that lets a patient go for a lower-cost upgrade but still feel that he's getting a higher technology. I've seen such initial-tier upgrades priced for as little as $200 to $300 per eye or close to $1,000 per eye if a femtosecond cataract laser is used. The patients sign an advanced beneficiary notice that acknowledges that the additional service isn't covered by insurance and that they will pay for it."

Dr. Dell also thinks multiple tiers are the way to go. "The way we approach it with our patients is to have three tiers: basic surgery covered by Medicare or insurance; a 'distance package' that typically involves an LRI, done by a laser or by hand, or a toric lens; and then a package we refer to by the copyrighted term 'Full Focus Cataract Surgery,' which corrects both distance and near vision." Like Mr. Pickett with his mailer, Dr. Dell says it's always best to speak in terms of benefits, not nuts and bolts of technologies. "We don't say, 'If you get this lens or this type of astigmatic correction, there will be one price, and if you get a different technology there will be another,' " he says. "We talk in terms of potential results. In truth, from a marketing standpoint, having three tiers will certainly mean that many patients won't pick the top tier, but the number who pick the bottom tier will also go down. Most patients, I think, will pick the middle or the top tier."

In addition to tiers, Mr. Pickett adds that some practices will offer initial diagnostic testing with advanced instruments—not usually reimbursed by Medicare—to help determine if someone is a candidate for premium lenses and which one might be best. "I've seen a $99-dollar package where the only thing the patient is paying for is the diagnostics outside the normal exams," he says. "I've seen the package consist of corneal topography and/or such technology as the OPD Scan from Nidek/Marco. The topography can detect irregularities and determine if the astigmatism is asymmetrical. Just make sure that you're upfront with what's on the ABN before doing such an upgrade, and describe what is, and isn't, considered included for normal cataract surgery."



Establishing an aesthetician room can generate cosmetic surgery referrals.

• ***Keep expectations in check.*** Though you want patients to be enthusiastic about premium lenses, you don't want them to be too excited and set themselves up for postop dissatisfaction. "I think the way to head off some of these problems is to have a frank discussion with the patient, saying, 'Here's what I think I can realistically deliver,' " Dr. Dell says. "We're very, very careful about underpromising what we can actually achieve with these implants, both in spoken and written communication. Regardless of the technology, I tell them that our goal is to reduce their need for glasses, but that it's unusual for us to completely eliminate it. And, when patients enter into the process thinking that this is our goal, the overwhelming majority of them are spectacle-free and are elated. And the ones who aren't spectacle-free get the result that they were told is the most likely outcome for them."

Cosmetic Offerings

Some practices may choose to range farther afield from just increasing their premium cataract offerings and may decide that there's additional revenue to be gained by offering their patients cosmetic treatments. Here, surgeons provide advice on the two most common treatments a "beginner" should start with: Botox and filler injections.

• ***Spread the word.*** If you're going to begin offering Botox and/or fillers to your patients, surgeons say you've got to let them know about it. Fortunately, they say, this doesn't have to be expensive. "It's mostly word-of-mouth," says Chicago ophthalmologist Adam Cohen, who performs a range of cosmetic procedures at his practice. "You have to be proactive and promote yourself. Pass your card out when you can, and set up relationships with health spas and salons. If you intend to spend some money on advertising, concentrate on the Internet and your website."

Cincinnati, Ohio, surgeon Jeffrey Nerad, a past president of the American Society of Ophthalmic Plastic and Reconstructive Surgery, says that ophthalmologists can often draw on their existing patients. "The advantage is we have patients coming into our office," he says. "The disadvantage is they don't necessarily expect you to offer Botox or fillers, so you have to promote those services in your waiting room and through your staff. It's a very competitive market, and you will have to compete against physicians who are spending thousands of dollars to set up posters along the interstate. This will be tough unless you can draw on your own patient population."

• ***Accommodate the patients.*** As more patients begin to come to your office for cosmetic procedures, surgeons say you will have to treat them differently than your average patient. "I'm half cosmetic and half functional patients now," explains Dr. Cohen. "It's tricky. You can't have a conventional medical office and think someone will come in for Botox or cosmetic surgery. You can't have an old phoropter and slit lamp in the room with some eye charts on the wall. Consider having a small room or area for meeting with these clients. Think about your waiting

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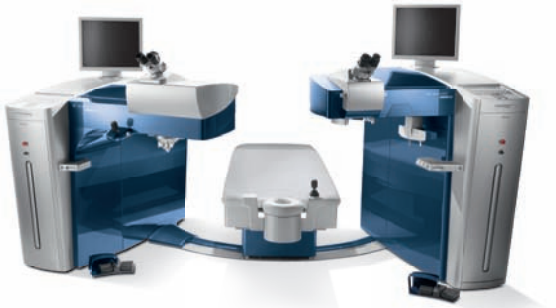

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Important Safety Information about the WaveLight® Excimer Laser Systems

This information pertains to all WaveLight® Excimer Laser Systems, including the WaveLight® ALLEGRETTO WAVE®, the ALLEGRETTO WAVE® Eye-Q , and the WaveLight® EX500.

Caution: Federal (U.S.) law restricts the WaveLight® Excimer Laser Systems to sale by or on the order of a physician. Only practitioners who are experienced in the medical mangement and surgical treatment of the cornea, who have been trained in laser refractive surgery (including laser calibration and operation) should use a WaveLight® Excimer Laser System.

Indications: FDA has approved the WaveLight® Excimer Laser for use in laser-assisted in situ keratomileusis (LASIK) treatments for:

- the reduction or elimination of myopia of up to - 12.0 DS and up to 6.0 D of astigmatism at the spectacle plane;
- the reduction or elimination of hyperopia up to + 6.0 DS with and without astigmatic refractive errors up to 5.0 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of + 6.0 D;
- the reduction or elimination of naturally occurring mixed astigmatism of up to 6.0 D at the spectacle plane; and
- the wavefront-guided reduction or elimination of myopia of up to -7.0 DS and up to 3.0 D of astigmatism at the spectacle plane.

The WaveLight® Excimer Laser Systems are only indicated for use in patients who are 18 years of age or older (21 years of age or older for mixed astigmatism) with documentation of a stable manifest refraction defined as ≤ 0.50 D of preoperative spherical equivalent shift over one year prior to surgery, exclusive of changes due to unmasking latent hyperopia.

Contraindications: The WaveLight® Excimer Laser Systems are contraindicated for use with patients who:

- are pregnant or nursing;
- have a diagnosed collagen vascular, autoimmune or immunodeficiency disease;
- have been diagnosed keratoconus or if there are any clinical pictures suggestive of keratoconus; or
- are taking isotretinoin (Accutane*) and/or amiodarone hydrochloride (Cordarone*).

Warnings: The WaveLight® Excimer Laser Systems are not recommended for use with patients who have:

- systemic diseases likely to affect wound healing, such as connective tissue disease, insulin dependent diabetes, severe atopic disease or an immunocompromised status;
- a history of Herpes simplex or Herpes zoster keratitis;
- significant dry eye that is unresponsive to treatment;
- severe allergies; or
- an unreliable preoperative wavefront examination that precludes wavefront-guided treatment.

The wavefront-guided LASIK procedure requires accurate and reliable data from the wavefront examination. Every step of every wavefront measurement that may be used as the basis for a wavefront-guided LASIK procedure must be validated by the user. Inaccurate or unreliable data from the wavefront examination will lead to an inaccurate treatment.

Precautions: The safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for patients with:

- progressive myopia, hyperopia, astigmatism and/or mixed astigmatism, ocular disease, previous corneal or intraocular surgery, or trauma in the ablation zone;
- corneal abnormalities including, but not limited to, scars, irregular astigmatism and corneal warpage;
- residual corneal thickness after ablation of less than 250 microns due to the increased risk for corneal ectasia;
- pupil size below 7.0 mm after mydriatics where applied for wavefront-guided ablation planning;
- history of glaucoma or ocular hypertension of > 23 mmHg;
- taking the medication sumatriptan succinate (Imitrex*);
- corneal, lens and/or vitreous opacities including, but not limited to cataract;
- iris problems including , but not limited to, coloboma and previous iris surgery compromising proper eye tracking; or
- taking medications likely to affect wound healing including (but not limited to) antimetabolites.

In addition, safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for:

- treatments with an optical zone < 6.0 mm or > 6.5 mm in diameter, or an ablation zone > 9.0 mm in diameter; or
- wavefront-guided treatment targets different from emmetropia (plano) in which the wavefront calculated defocus (spherical term) has been adjusted;

In the WaveLight® Excimer Laser System clinical studies, there were few subjects with cylinder amounts > 4 D and ≤ 6 D. Not all complications, adverse events, and levels of effectiveness may have been determined for this population.

Pupil sizes should be evaluated under mesopic illumination conditions. Effects of treatment on vision under poor illumination cannot be predicted prior to surgery.

Adverse Events and Complications

Myopia: In the myopia clinical study, 0.2% (2/876) of the eyes had a lost, misplaced, or misaligned flap reported at the 1 month examination.

The following complications were reported 6 months after LASIK: 0.9% (7/818) had ghosting or double images in the operative eye; 0.1% (1/818) of the eyes had a corneal epithelial defect.

Hyperopia: In the hyperopia clinical study, 0.4% (1/276) of the eyes had a retinal detachment or retinal vascular accident reported at the 3 month examination.

The following complications were reported 6 months after LASIK: 0.8% (2/262) of the eyes had a corneal epithelial defect and 0.8% (2/262) had any epithelium in the interface.

Mixed Astigmatism: In the mixed astigmatism clinical study, two adverse events were reported. The first event involved a patient who postoperatively was subject to blunt trauma to the treatment eye 6 days after surgery. The patient was found to have an intact globe with no rupture, inflammation or any dislodgement of the flap. UCVA was decreased due to this event. The second event involved the treatment of an incorrect axis of astigmatism. The axis was treated at 60 degrees instead of 160 degrees.

The following complications were reported 6 months after LASIK: 1.8% (2/111) of the eyes had ghosting or double images in the operative eye.

Wavefront-Guided Myopia: No adverse events occurred during the postoperative period of the wavefront-guided LASIK procedures. In the Control Cohort (traditional LASIK treatment) one subject undergoing traditional LASIK had the axis of astigmatism programmed as 115 degrees instead of the actual 155 degree axis. This led to cylinder in the left eye.

The following complications were reported 6 months after wavefront-guided LASIK in the Study Cohort: 1.2% (2/166) of the eyes had a corneal epithelial defect; 1.2% (2/166) had foreign body sensation; and 0.6% (1/166) had pain. No complications were reported in the Control Cohort.

Clinical Data

Myopia: The myopia clinical study included 901 eyes treated, of which 813 of 866 eligible eyes were followed for 12 months. Accountability at 3 months was 93.8%, at 6 months was 91.9%, and at 12 months was 93.9%. Of the 782 eyes eligible for the uncorrected visual acuity (UCVA) analysis of effectiveness at the 6-month stability time point, 98.3% were corrected to 20/40 or better, and 87.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: visual fluctuations (28.6% vs. 12.8% at baseline).

Long term risks of LASIK for myopia with and without astigmatism have not been studied beyond 12 months.

Hyperopia: The hyperopia clinical study included 290 eyes treated, of which 100 of 290 eligible eyes were followed for 12 months. Accountability at 3 months was 95.2%, at 6 months was 93.9%, and at 12 months was 69.9%. Of the 212 eyes eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 95.3% were corrected to 20/40 or better, and 69.4% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "much worse" at 6 months post-treatment: halos (6.4%); visual fluctuations (6.1%); light sensitivity (4.9%); night driving glare (4.2%); and glare from bright lights (3.0%).

Long term risks of LASIK for hyperopia with and without astigmatism have not been studied beyond 12 months.

Mixed Astigmatism: The mixed astigmatism clinical study included 162 eyes treated, of which 111 were eligible to be followed for 6 months. Accountability at 1 month was 99.4%, at 3 months was 96.0%, and at 6 months was 100.0%. Of the 142 eyes eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 97.3% achieved acuity of 20/40 or better, and 69.4% achieved acuity of 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: sensitivity to light (52.9% vs. 43.3% at baseline); visual fluctuations (43.0% vs. 32.1% at baseline); and halos (42.3% vs. 37.0% at baseline).

Long term risks of LASIK for mixed astigmatism have not been studied beyond 6 months.

Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). 166 of the Study Cohort and 166 of the Control Cohort were eligible to be followed at 6 months. In the Study Cohort, accountability at 1 month was 96.8%, at 3 months was 96.8%, and at 6 months was 93.3%. In the Control Cohort, accountability at 1 month was 94.6%, at 3 months was 94.6%, and at 6 months was 92.2%.

Of the 166 eyes in the Study Cohort that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 93.4% were corrected to 20/20 or better. Of the 166 eyes in the Control Cohort eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 92.8% were corrected to 20/20.

In the Study Cohort, subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: light sensitivity (47.8% vs. 37.2% at baseline) and visual fluctuations (20.0% vs. 13.8% at baseline). In the Control Cohort, the following visual symptoms were reported at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: halos (45.4% vs. 36.6% at baseline) and visual fluctuations (21.9% vs. 18.3% at baseline).

Long term risks of wavefront-guided LASIK for myopia with and without astigmatism have not been studied beyond 6 months.

Information for Patients: Prior to undergoing LASIK surgery with a WaveLight® Excimer Laser System, prospective patients must receive a copy of the relevant Patient Information Booklet, and must be informed of the alternatives for correcting their vision, including (but not limited to) eyeglasses, contact lenses, photorefractive keratectomy, and other refractive surgeries.

Attention: Please refer to a current WaveLight® Excimer Laser System Procedure Manual for a complete listing of the indications, complications, warnings, precautions, and side effects.

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room also: It's really something that's very important, because you want the patients to have a positive impression right away. Rather than have a separate waiting room for your cosmetic and 'regular' patients, though, maybe just consider spacing them out so they don't overlap."

Dr. Nerad says only to go high-end if you find success with current patients. "We have separate entrances and exits for pre- and postop patients, and a spa area for self-pay vs. the waiting area for insurance patients," he says. "All that's good, but if you're just starting, it would be a considerable expense that you'd have to weigh against the money you're going to recoup."

Once the cosmetic patient is in front of you, surgeons say to be prepared to spend some time. "If you're not established in cosmetic procedures, you should be happy about anyone who comes in," says Dr. Cohen. "They have a lot of choices out there. You have to take some time and establish a rapport, because they're there about an elective service. You have to explain their options and ask them what's bothering them. You also have to explain that you might not be able to give them what they want if it's not reasonable medically."

• ***Botox.*** Surgeons say that, since Botox has been commoditized, a lot of the success with it revolves around pricing. "Every kind of health-care provider does Botox and fillers now," says Dr. Nerad. "This includes nurses and dentists. I even had a patient who was getting Botox from his cardiac surgeon. Patients shop for the cheapest price."

Dr. Cohen breaks the pricing down: "You may be doing it for $12 per unit, and there are 100 units in bottle, so you'll make $1,200," he says. "A bottle of Botox costs $525, bringing you down to making $675. Subtract $25 or $30 for supplies and you're making around $625. So, you have to sell a lot of Botox to really make a go of it, since you can make around $600 for a cataract that takes 10 minutes. The other consideration is, Botox patients come back to you and say that it's not working and they want more, so you wind up giving a little more of it for free because it makes good business sense."

• ***Fillers.*** Dr. Nerad says that, unlike Botox, there are various types of fillers to choose from, and it's in the physician's best interest to start with the most benign. "There are a number of reversible fillers that have a high safety index—the hyaluronic acid-based fillers," he explains. "Hyaluronic acid is a natural material that's found in the human body, and the safer fillers are the HA fillers like Restylane, Juvederm and Expressions. The problem is that HA fillers are relatively short-acting, lasting roughly six months. To increase the duration of action, manufacturers will put additional materials in, such as the filler Radiesse, which uses calcium particles to extend its life; or Artefill, which uses plastic microspheres. However, any time you add an unnatural product to a filler, it has the potential to create problems in which your body reacts to the filler, causing inflammation.

"At the far end of the spectrum of duration is injecting the patient's own fat," Dr. Nerad continues. "But this is a procedure most ophthalmologists shouldn't enter lightly, since it involves liposuction and is more involved. That's why I advise the general ophthalmologist to start with safe fillers like the HA-based ones. Once they establish the clientele, or they feel they know what they're doing, they can add something more complicated."

In terms of pricing, Dr. Cohen says he charges $650 per tube of filler. "Some people charge $600, and some charge $550, depending on how they want to work it," he says. "A tube costs $240, leaving around $410 of profit. Effective pricing is also dependent on your location and who you are in the cosmetic realm. If you're well-known, you'll get more of a premium than someone who's up-and-coming."

• ***Aestheticians.*** If you have the space and the patients, one move some physicians make is to add an aesthetician's cosmetic services. "I have quite a few aestheticians," says Dr. Cohen. "We have rotating aestheticians who move through various practice locations. Some work on salary, and some on commission. They can be successful, but they require a separate room that's tailored to fulfill the needs of patients. The room needs a nice table, a waxing machine, a variety of skin peels, cosmeceuticals, sundry inventory, towels and a towel warmer. It's a spa room; it can't be anything else. The room can cost between $1,500 and $5,000 to create, depending on how much you want to offer."

Dr. Nerad says that, in his experience, the main benefit of the aesthetician has been as a feeder for his surgical services. "I have a medi-spa sort of setting with three aestheticians," he says. "Basically, it's kind of a break-even deal. Selling products and the aesthetician's services pay for themselves, but the way it makes revenue is through what it generates for me in terms of referrals for surgery like blepharoplasties. There's potential there, but it's competitive."

Dr. Nerad says that, though offering cosmetic services may seem like a daunting new direction, ironically, the chemicals used the most are actually closely tied to ophthalmology. "I mention to patients that hyaluronic acid and Botox were both developed by ophthalmologists," he says. "The first Botox injection was used by Alan Scott for cross-eyed children in the 80s and then for treating blepharospasm, and Healon is a type of hyaluronic acid that's been used in cataract surgery for a long time. So, there's a long history of the use of these products by eye surgeons. However, for ophthalmologists, I caution that this is no guarantee of success." REVIEW

Stuck With a Lemon: When Your EHR Fails

Christopher Kent, Senior Editor

What to do when your electronic records system isn't meeting your needs—orwo rse.

Switching from paper records to electronic records would be a challenging feat, even if electronic records were flawlessly designed and perfectly met a practice's needs. Given that today's EHR programs still leave much to be desired—and many different software and hardware systems are competing for your money—it should be no surprise that many practices do not end up staying with their first EHR system.

In fact, a wide range of studies and surveys are finding significant levels of dissatisfaction among EHR users, both in medicine in general and in ophthalmology in particular. Research firm KLAS published a study in 2012 that found that 50 percent of EHR system sales were made to replace existing systems; among practices with more than 10 physicians, about two-thirds of EHR system purchases were replacements for existing systems. The numbers in some reports are a little smaller: A December 2012 survey by HIMSS Analytics found that more than 30 percent of medical providers were planning to replace their EHR systems. (Reasons cited include missing features, cumbersome user interfaces and hardware problems.) A poll of 17,000 EHR users conducted by Black Book Rankings, a marketing research firm, found that 17 percent of healthcare organizations were ready to change to a different system. Notably, specialists were more unhappy than general physicians.

Dissatisfaction also seems to be increasing over time. The American College of Physicians and American EHR Partners reviewed data from multiple surveys of 4,279 clinicians conducted between March 2010 and December 2012. They found that user satisfaction declined 12 percent from 2010 to 2012, and the percentage of clinicians who would not recommend their system to a peer increased from 24 percent in 2010 to 39 percent in 2012. Reasons for dissatisfaction included long-lasting reductions in patient throughput: In 2012, 32 percent of the responders said they had not returned to normal productivity. Furthermore, dissatisfaction with their systems' ease of use increased from 23 percent in 2010 to 37 percent in 2012. However, there are some signs of hope: A 2011 Centers for Disease Control and Prevention study of physicians (generalists and specialists) reported that 85 percent of physicians were somewhat or very satisfied with their EHR system, and 71 percent said they'd buy their system again.

However you interpret the numbers, it's clear that finding a satisfactory EHR system can be fraught with

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peril—and many doctors end up not staying with the system they started with. Here, two practices who decided to change EHR systems share their stories, and a practice management expert offers advice based on his experience in the field.

Not an Easy Transition

"EHR systems have been available in one form or another for more than 20 years," observes John Pinto, president of J. Pinto & Associates. "The systems have been improving every year, but if they were easy to use and economically trivial we would have seen a wholesale conversion to EHR 20 years ago. Obviously, that hasn't happened. Half of the existing ophthalmology practices in this country have not made the conversion—or have made the conversion and then gone back to paper."

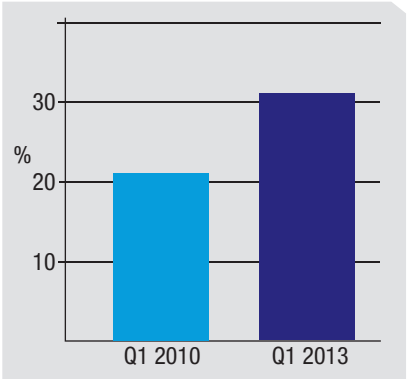
Despite this, Mr. Pinto says that the vast majority of the practices he works with have stayed with their EHR systems. "That may be partly because I work with a skewed sample of practices," he notes. "I tend to be hired by successful practices. In the past decade, I would say that no more than 5 percent of the practices I've worked with have adopted a system and then had to switch to a different system. Of the remaining practices, I'd say about half continue to have chronic challenges, large or small, with the system they use, and are still trying to make it work better for them. The other half are up to speed and running just fine."

Nevertheless, many practices do end up having to switch EHR systems, as the two following stories confirm.

A Patient Data Disaster

"We were an early adopter of EHR," says Audrey Gyoerkoe, practice administrator at Kelly Eye Center in Raleigh, N.C. "We began using an electronic management system from a very small company when we opened the practice about 12 years ago, before all of the regulations and requirements. In recent years we realized that our original system would not provide what we were going to need in the future, so we decided to upgrade.

Percentage of EHR Buyers Replacing an Existing System



A survey of 385 medical personnel actively shopping for an EHR system, conducted by the company Software Advice, found a significant jump between 2010 and 2013 in the percentage of shoppers replacing an existing system.

"We looked at a couple of systems at a trade show and decided to go with one of the bigger companies," she says. "We're a small practice—two doctors and about 16 employees, some of whom are part-time—but we chose to go with a big vendor that was popular and advertising heavily at the trade shows. We could have gone through a third-party vendor, who essentially buys the rights to the big company's software and works with you and provides services, but we chose to go directly with the big company.

"As it turned out, the big company was not really set up to work with a small practice," she continues. "If you were a really big practice with 200 employees or more, the company typically assigned you a specific person who would help you through everything. But because we were a small practice, they didn't. In spite of that, because we were early adopters, we thought we'd be really comfortable going into a second system.

"Unfortunately, we were live for one week when the entire system crashed," she says. "Even worse, the crash wiped out our old system as well. All of our patient data was simply gone, and the company made no effort to recover our data. Our hardware guys actually paid to send the files to the FBI Data Recovery Service, in hopes we could get something back, but even they couldn't recover anything. So when patients came in the door, we had no idea who they were, what their appointment time was, which doctor they were there to see or what their insurance coverage was. For six months we had a crew here, not only rebuilding the software and getting it reinstalled, but going through everything that happened during that six-month period. They had to re-enter the charges and re-post the checks in order to file insurance, or bill the patient, or know when that patient's next appointment was going to be."

Ms. Gyoerkoe says they nevertheless stayed with the big company for a number of years after the crash. "That's because we'd invested a lot of money, especially after the crash," she explains. "We probably spent close to $100,000 trying to recover the data and get through that six-month period. The system itself is reasonably good; it's more advanced than most at this point, I think, and very well-accepted. The vendor has a lot of happy customers. But for the most part, those customers are either much larger practices with a person assigned to help them, or they're smaller practices that went through a third party.

"Eventually we switched to a much smaller EHR company, and that transition went much better," she adds. "Unfortunately, many issues surrounding the crash are still unresolved. We're still getting bills and e-mails about it, and there's never been a sign-off on our account."

Trying the Cloud

Most unhappy EHR stories are less catastrophic than that one, but still enlightening. Patrick Hageman, MD, owner of Kernersville Eye Surgeons in Kernersville, N.C., who first used EHR during his residency training, started his practice right out of residency. "We used EHR from the outset," he says. "That actually went pretty well—but every EHR system has some hiccups and limitations and unforeseen expenses. That first EHR system was a hosted software service solution. Basically, it was like renting or leasing the system, which the company hosts on their server in the cloud. We paid about $2,000 a month for it.

"That system had a fairly large ophthalmology following," he continues. "It wasn't specifically designed for ophthalmology, but it did have a lot of templates that were ophthalmology-friendly. The vendor had a pretty good reputation, so we decided to go with them. The fact that the data was in the cloud also provided a cost advantage when we were starting up our new practice; we didn't have to purchase a server or the software. Purchasing the software would have cost $80,000, which is a large sum of money for two guys right out of residency starting an ophthalmology practice."

Dr. Hageman notes that he didn't care for the EHR system they used when he was a resident. "We didn't think it was well-designed, even though it was ophthalmology-specific," he says. "It did what it needed to do, but we felt that it was haphazardly put together. Every screen was different. The close button wasn't always in the same place; the save button wasn't always in the same place. Issues like that made it very cumbersome and inefficient to go from screen to screen, so we decided not to use that system."

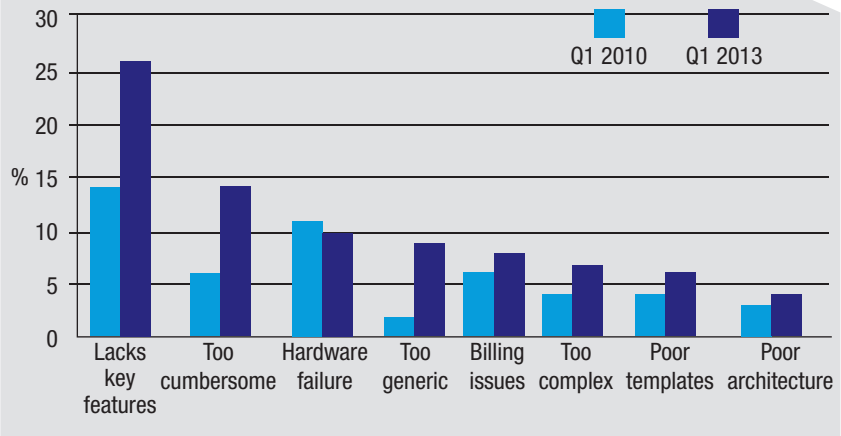
Nevertheless, once he'd purchased the cloud-based EHR system, it didn't take too long for Dr. Hageman to discover limitations. "One of the problems we encountered was difficulty interfacing with our equipment," he says. "Initially the vendor promised that the system would interface with our equipment, but it turned out that they overpromised and underdelivered—something I find a lot of companies do. There were also a lot of headaches associated with the cloud. A server is nice to have in the office when you need to put other things on there that your employees need to have access to. We didn't have that functionality with this solution.

"We eventually did work through the interface issues, but I still found the system to be inefficient," he continues. "So, I made the decision last year to switch over to an EHR that was specific for ophthalmology. We'd bring everything in-house, have our own server and purchase the software. I thought that an ophthalmology-specific system would have more efficiencies built into it for documenting patient encounters."

Dr. Hageman notes that this meant making a fairly big investment, so they chose a less-expensive option to mitigate the impact on their cash flow. "The software cost us about $30,000, including the cost of the server, so it was much more affordable than it would have been to purchase the previous system's software. The maintenance fees were much cheaper, too. Ultimately, the cost for our two-physician practice using the first, hosted system and the adjunct image-management system was about $30,000 per year. Now we've purchased a new system outright for $30,000, and our maintenance fees are about $5,000 per year. So, this will lead to substantial savings over the long haul."

Dr. Hageman says that the new system is designed specifically for ophthalmology, and that does have several significant advantages. "The previous system couldn't manage images," he says. "Paying for the separate image-management system was really getting expensive. The new system can handle all of the images—at least, when the interfaces are working. Also, the ability to document some things specific to ophthalmology has been helpful."

Reasons for Dissatisfaction with an Existing EHR System



According to survey data collected by Software Advice, the number of EHR shoppers saying they were unhappy with their current EHR system grew by 6.5 percentage points between the first quarter of 2010 and Q1 2013; reasons cited are summarized above.

Not Out of the Woods

However, Dr. Hageman says that the latest transition has not gone smoothly. "That's the headache that

For the treatment of elevated IOP

UNLOCK TREATMENT POSSIBILITIES

SIMBRINZA™ Suspension provided additional 1-3 mm Hg IOP lowering compared to the individual components[1]

- IOP measured at 8 AM, 10 AM, 3 PM, and 5 PM was reduced by **21-35%** at Month 3[2-4]
- Efficacy proven in two pivotal Phase 3 randomized, multicenter, double-masked, parallel-group, 3-month, 3-arm, contribution-of-elements studies[2,3]
- The most frequently reported adverse reactions (3-7%) in a six month clinical trial were eye irritation, eye allergy, conjunctivitis, blurred vision, dysgeusia (bad taste), conjunctivitis allergic, eye pruritus, and dry mouth[5]
- Only available beta-blocker-free fixed combination[2,3]

INDICATIONS AND USAGE

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination indicated in the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dose is one drop of SIMBRINZA™ Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA™ Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

IMPORTANT SAFETY INFORMATION

Contraindications

SIMBRINZA™ Suspension is contraindicated in patients who are hypersensitive to any component of this product and neonates and infants under the age of 2 years.

Warnings and Precautions

Sulfonamide Hypersensitivity Reactions—Brinzolamide is a sulfonamide, and although administered topically, is absorbed systemically. Sulfonamide attributable adverse reactions may occur. Fatalities have occurred due to severe reactions to sulfonamides. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Corneal Endothelium—There is an increased potential for developing corneal edema in patients with low endothelial cell counts.

Severe Hepatic or Renal Impairment (CrCl <30 mL/min)—SIMBRINZA™ Suspension has not been specifically studied in these patients and is not recommended.

Adverse Reactions

In two clinical trials of 3 months' duration with SIMBRINZA™ Suspension, the most frequent reactions associated with its use occurring in approximately 3-5% of patients in descending order of incidence included: blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Adverse reaction rates with SIMBRINZA™ Suspension were comparable to those of the individual components. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA™ Suspension patients.

Drug Interactions—Consider the following when prescribing SIMBRINZA™ Suspension:

Concomitant administration with oral carbonic anhydrase inhibitors is not recommended due to the potential additive effect. Use with high-dose salicylate may result in acid-base and electrolyte alterations. Use with CNS depressants may result in an additive or potentiating effect. Use with antihypertensives/cardiac glycosides may result in additive or potentiating effect on lowering blood pressure. Use with tricyclic antidepressants may blunt the hypotensive effect of systemic clonidine and it is unknown if use with this class of drugs interferes with IOP lowering. Use with monoamine oxidase inhibitors may result in increased hypotension.

For additional information about SIMBRINZA™ Suspension, please see Brief Summary of full Prescribing Information on adjacent page.

Learn more at myalcon.com/simbrinza

SIMBRINZA™
(brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

ONE BOTTLE. MANY POSSIBILITIES.

References: 1. SIMBRINZA™ Suspension Package Insert. **2.** Katz G, DuBiner H, Samples J, et al. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2% [published online ahead of print April 11, 2013]. *JAMA Ophthalmol.* doi:10.1001/jamaophthalmol.2013.188. **3.** Nguyen QH, McMenemy MG, Realini T, et al. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *J Ocul Pharmacol Ther.* 2013;29(3):
290-297. **4.** Data on file, 2013. **5.** Whitson JT, Realini T, Nguyen QH, McMenemy MG, Goode SM. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. *Clin Ophthalmol.* 2013;7:1053-1060.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of SIMBRINZA™ Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA™ Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

DOSAGE FORMS AND STRENGTHS

Suspension containing 10 mg/mL brinzolamide and 2 mg/mL brimonidine tartrate.

CONTRAINDICATIONS

Hypersensitivity - SIMBRINZA™ Suspension is contraindicated in patients who are hypersensitive to any component of this product.

Neonates and Infants (under the age of 2 years) - SIMBRINZA™ Suspension is contraindicated in neonates and infants (under the age of 2 years*) see Use in Specific Populations*

WARNINGS AND PRECAUTIONS

Sulfonamide Hypersensitivity Reactions - SIMBRINZA™ Suspension contains brinzolamide, a sulfonamide, and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of SIMBRINZA™ Suspension. Fatalities have occurred due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation *[see Patient Counseling Information]*

Corneal Endothelium - Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing SIMBRINZA™ Suspension to this group of patients.

Severe Renal Impairment - SIMBRINZA™ Suspension has not been specifically studied in patients with severe renal impairment (CrCl < 30 mL/min). Since brinzolamide and its metabolite are excreted predominantly by the kidney, SIMBRINZA™ Suspension is not recommended in such patients.

Acute Angle-Closure Glaucoma - The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. SIMBRINZA™ Suspension has not been studied in patients with acute angle-closure glaucoma.

Contact Lens Wear - The preservative in SIMBRINZA™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA™ Suspension but may be reinserted 15 minutes after instillation *[see Patient Counseling Information]*.

Severe Cardiovascular Disease - Brimonidine tartrate, a component of SIMBRINZA™ Suspension, has a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Severe Hepatic Impairment - Because brimonidine tartrate, a component of SIMBRINZA™ Suspension, has not been studied in patients with hepatic impairment, caution should be exercised in such patients.

Potentiation of Vascular Insufficiency - Brimonidine tartrate, a component of SIMBRINZA™ Suspension, may potentiate syndromes associated with vascular insufficiency. SIMBRINZA™ Suspension should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangitis obliterans.

Contamination of Topical Ophthalmic Products After Use - There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information]*.

ADVERSE REACTIONS

Clinical Studies Experience - 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.

SIMBRINZA™ Suspension - In two clinical trials of 3 months duration 435 patients were treated with SIMBRINZA™ Suspension, and 915 were treated with the two individual components. The most frequently reported adverse reactions in patients treated with SIMBRINZA™ Suspension occurring in approximately 3 to 5% of patients in descending order of incidence were blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Rates of adverse reactions reported with the individual components were comparable. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA™ Suspension patients.

Other adverse reactions that have been reported with the individual components during clinical trials are listed below.

Brinzolamide 1% - In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

Brimonidine Tartrate 0.2% - In clinical studies of brimonidine tartrate 0.2%, adverse reactions occurring in approximately 10 to 30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Reactions occurring in approximately 3 to 9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

Postmarketing Experience - The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia.

Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions *[see Contraindications]*.

DRUG INTERACTIONS

Oral Carbonic Anhydrase Inhibitors - There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide ophthalmic suspension 1%, a component of SIMBRINZA™ Suspension. The concomitant administration of SIMBRINZA™ Suspension and oral carbonic anhydrase inhibitors is not recommended.

High-Dose Salicylate Therapy - Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide ophthalmic suspension 1%. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving SIMBRINZA™ Suspension.

CNS Depressants - Although specific drug interaction studies have not been conducted with SIMBRINZA™, the possibility of an additive or potentiating effect with CNS depressants (alcohol, opiates, barbiturates, sedatives, or anesthetics) should be considered.

Antihypertensives/Cardiac Glycosides - Because brimonidine tartrate, a component of SIMBRINZA™ Suspension, may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with SIMBRINZA™ Suspension is advised.

Tricyclic Antidepressants - Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with SIMBRINZA™ Suspension in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors - Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy - *Pregnancy Category C:* Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 60, and 120 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (180 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

Developmental toxicity studies performed in rats with oral doses of 0.66 mg brimonidine base/kg revealed no evidence of harm to the fetus. Dosing at this level resulted in a plasma drug concentration approximately 100 times higher than that seen in humans at the recommended human ophthalmic dose. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent.

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

Nursing Mothers - In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (150 times the recommended human ophthalmic dose) were observed during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. In animal studies, brimonidine was excreted in breast milk.

It is not known whether brinzolamide and brimonidine tartrate are excreted in human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use - The individual component, brinzolamide, has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine tartrate, has been studied in pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in patients 2 to 6 years old. SIMBRINZA™ Suspension is contraindicated in children under the age of 2 years *[see Contraindications]*.

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

OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following an oral overdose of brinzolamide. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse event reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine as part of medical treatment of congenital glaucoma or by accidental oral ingestion. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

PATIENT COUNSELING INFORMATION

Sulfonamide Reactions - Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

Temporary Blurred Vision - Vision may be temporarily blurred following dosing with SIMBRINZA™ Suspension. Care should be exercised in operating machinery or driving a motor vehicle.

Effect on Ability to Drive and Use Machinery - As with other drugs in this class, SIMBRINZA™ Suspension may cause fatigue and/or drowsiness in some patients. Caution patients who engage in hazardous activities of the potential for a decrease in mental alertness.

Avoiding Contamination of the Product - Instruct patients that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can 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 *[see Warnings and Precautions]*. Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

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

Concomitant Topical Ocular Therapy - If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

Contact Lens Wear - The preservative in SIMBRINZA™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA™ Suspension, but may be reinserted 15 minutes after instillation.

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we're in the middle of right now," he explains. "This is different from when we were opening our practice, because this time I have a lot of data collected over a three-year period that was stored in our first EHR system. I wanted that data to be converted into the new system.

"I spoke to three or four vendors to see which system would be the best fit for us," he continues. "One of the companies wouldn't promise to convert the data, but another one said, 'Sure, we can do that for you. You won't have to worry about it.' That was the company we decided to go with.

"Unfortunately, that really didn't happen," he says. "Today, we're still waiting for them to convert a lot of our data. This has left us in a difficult situation, because I'm still renting the previous system. I don't own their software, so when my contract ends, I won't have access to my data anymore. They could actually give it to me on a hard drive, but I still wouldn't be able to access it because I don't own the software.

"Now I'm trying to figure out a way to manage this," he says. "There are companies out there that will archive the data for you so you can read it, but that costs about $20,000. That's an expense I wasn't planning on."

Dr. Hageman says the new vendor also overpromised on the system's ability to interface with his instruments, just like the previous vendor did. "Getting all of those interfaces up and running on the latest system took about three or four times as long as we had anticipated," he says. "It was just as difficult with the new system as with the old. I was very adamant when talking with the new company about this concern. I told them I'd had this problem with the first EHR implementation, and that I was really worried that this wasn't going to go well. They said, 'Oh no, we've done this before. No problem.' When we went live, none of the interfaces worked … not one! It took a couple of weeks to get them working. It was very frustrating.

"When we implemented the first system, we were a brand new practice, so we weren't very busy," he adds. "Because of that, the problems we had were not a big deal. Now I'm much busier, so these problems are really impacting my work flow. I actually had to stop using the new system for the first week and go back to using the old system so we could function until we got those interfaces up and running."

> *"Your investment is not just dollars, it's time and effort and your patient information."*
> *—Patrick Hageman, MD*

Despite all the problems he's had to deal with, Dr. Hageman is optimistic. "In the long run, I think this current transition will be worth it," he says. "A year from now, I'll probably be really happy that I did it. But right now I'm in the middle of the chaos, trying to get everything working properly."

Selecting the Right System

Clearly, the best way to avoid ending up in trouble is to be very cautious when picking your EHR system in the first place. These strategies may help:

• ***Don't make low price your chief criterion.*** "If your selection criterion is that you want the lowest-cost system, you're likely to be disappointed," says Mr. Pinto. "It takes a lot of money to muster this kind of service offering. The low-cost providers tend to be people who have not penetrated the ophthalmic market, or are just starting a company out of their garage and you're going to be their third or fifth customer. They simply don't have the resources. And, they're not likely to be around in five years."

It's also important to remember that you're not just investing money. "In my mind, it seemed like switching to another system later, if necessary, was a better option than making a huge investment up front," says Dr. Hageman, talking about his first purchase. "On the other hand, we did make a big investment of a different sort when you consider having to convert all of our data and being able to access it. There are a lot of hidden costs when adopting EHR. Also, I underestimated how difficult the transition might be when switching from one system to another. Your investment is not just dollars, it's time and effort and your patient information."

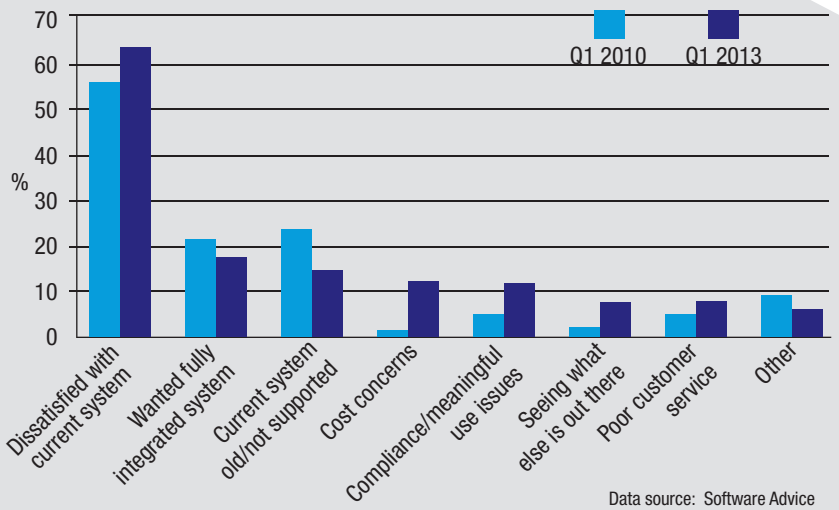
• ***Look for a top system with a solid track record.*** "There are a about half-dozen leading systems out there," notes Mr. Pinto. "The primary criteria that anyone should use when selecting an EHR system are to go with one of the lead vendors, and make sure that they have hundreds of ophthalmic installations that have been active for a year or longer. If you haven't done this, and you're six months post-install and it's not working out, call the vendor and find out how many ophthalmic customers they have that have been installed for over a year. If it's fewer than 100, you may have to bite the bullet and change vendors.

"That one-year figure seems to be critical," he continues, "because until that first year post-adoption has passed, it's not unusual for new users to say, 'This was a mistake.' If a system is making it past the one-year mark with hundreds of prior customers, that's a good omen that it will work in your practice, too."

On the other hand …

• ***Bigger isn't always better.*** As Ms. Gyoerkoe noted, their practice didn't benefit from the fact that the vendor they chose was large. Simi-

Reasons for Replacing an EHR System



larly, Dr. Hageman's first EHR choice was influenced by the vendor having a large market share, but that turned out not to be a guarantee of an ideal match, either. "We wanted to make sure the company was going to stick around," he explains. "This was before the meaningful use requirements came out; we wanted to make sure the company would be able to meet those criteria. I think if it had been a year later, we would have felt better about going with a smaller company that was less expensive. Another practice in our area that did choose a smaller vendor has been able to meet the meaningful use reimbursements; they're doing fine with that system."

At the same time, Dr. Hageman acknowledges that a larger company can have some advantages. "The first company we went with had a lot of staff, so when we had a problem, that problem was tracked and followed-up until it was resolved," he says. "Our current vendor has just a few employees, so they're not really equipped to stay on top of our problems. As a result, I constantly have to remind them until a problem is fixed."

• ***Consider the downside before purchasing a system in the cloud***. "There are some drawbacks there," notes Dr. Hageman. "You don't own your own data; and if you ever decide to change EHR systems in the future, there's a hidden cost—you'll have to archive your data so you can get access to it."

• ***Mac- and PC-based systems both have advantages.*** "Apple computers are well-known for having user-friendly interfaces," observes Dr. Hageman. "Everything is in the same place on every screen. You know where to close out, you know where the dialog box is. That's much better than what some platforms offer. However, most of the diagnostic equipment used in ophthalmology runs on Windows-based computers; so when you interface them with a different operating system, it becomes tricky. That concern kept us from choosing an Apple-based system. However, we know of another practice that's having success with one of those systems."

• ***Take future data access into consideration.*** "Make sure the EHR system you're switching to can actually convert your data," says Dr. Hageman. "If they can't, you have to consider what you're going to do to access the data that's hosted on your previous system. You'll have to have a way to access that data several years from when you used it—if you get audited, for example."

Doing Your Homework

Once you narrow the field, proceed with caution.

• ***Make a list of questions to ask, addressing everyone's needs.*** "Speak to as many current users as possible," Ms. Gyoerkoe advises. "Get a lot of references. And make a list of questions to ask, including issues that might affect everyone in your practice—your techs, your administrators, the doctors. You want to try to find out how a given EHR system will affect everyone in your practice."

• ***Remember that user opinions may be influenced by the size of their investment***. "Most of the people I know went with an EHR system and stuck with it; they haven't switched," says Dr. Hageman. "Several of them are using the system we started with, but they chose to purchase it—they didn't opt for a service arrangement the way we did. They seem to be happy with it. However, that may also be affected by the fact that they made a very large investment. Once you've sunk a significant amount of money into an EHR system, you may be willing to put up with limitations more than someone who's renting."

• ***Don't believe everything a vendor promises.*** "When you're buying your first EHR system, companies are going to promise that they can do a lot of things," notes Dr. Hageman. "You have to be very cautious about believing what they're promising and consider whether or not it's realistic. We were very naïve about that with the first system we went with. I thought I was a little more savvy the second time around, but I didn't really follow through with the company when I was questioning them on the ease they claimed they'd have setting up our interfaces. I'd be especially cautious if they say they can interface all of your

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• ***If a system seems promising, visit two practices similar to your own that are already using it.*** "It's absolutely critical that a delegation from your practice visits at least two practices that are already using the system you're planning to purchase," says Mr. Pinto. "And, this delegation must include one or more lead physicians from your group.

"You want to go to these practices and see the system being used live, used effectively and with happy customers," he continues. "That's the only thing that's going to give you any kind of peace of mind when you're a week or a month or six months into implementation, and you're pulling your hair out, as you almost certainly will be in the early months of adoption—no matter what vendor you pick. It's incredibly important to go into this with the confidence that another practice like yours has been able to get over the hurdle using your EHR system."

Making Sure You're Covered

Once you're ready to sign a contract:

• ***Make sure you will have universally accessible copies of your patient data.*** "At the meetings I attend, everyone is focused on asking other practices about their experience," says Ms. Gyoerkoe. "But I don't think anyone is asking: What happens if something goes wrong? People aren't thinking about the downside."

Ms. Gyoerkoe notes that most systems provide a template for patient data constructed using their software, which is different from a simple, universally accessible copy of the data. The former can be manipulated, but it can only be accessed using the company's proprietary software. The latter is simply a copy of the record—it can't be altered or updated—but it ensures that you'll always have access to your patient data. "Ideally, your vendor should make it easy for you to create copies of the patient data in a format that can easily be scanned into a new system," she says. "You need to have enough accessible data to survive an audit. Most systems don't do this automatically.

"We had nothing in our contract addressing the possibility of a major loss of data," she adds. "Nothing in our contract guaranteed access to our data, and nothing talked about what would happen if we needed to switch to another vendor. There was no strategy for recreating our data in the event of a breakdown."

> *"Your vendor should make it easy for you to create copies of patient data in a format that can easily be scanned into a new system."*
> *—Audrey Gyoerkoe*

• ***Have an exit strategy built into your contract.*** "If you have to switch companies because you're unhappy, or you have a capacity problem, or because there's a rule change and your vendor can't handle it, what is the strategy for moving all of that patient and demographic information into a new system?" asks Ms. Gyoerkoe. "These companies don't speak to one another, and they don't all speak the same language. So you can't easily take a patient file and transfer it into completely different software and expect to have full access to that record. This concern needs to be addressed in the contract you sign up front."

Getting Off to a Good Start

Even if you pick the best EHR system in the world, you need to undertake implementation with some key things in mind:

• ***Make sure you have physician support for the system in your practice.*** "In my experience, nine times out of 10, if a client has picked one of the top vendors with more than 100 systems active for a year or more, and the system is not working for them after six months, it's usually the client's problem, not the vendor's," says Mr. Pinto. "One key issue that can lead to problems is disengagement on the part of the doctors—i.e., they made the decision to go to EHR and then turned to the staff and said, 'OK, make it happen for us, guys.' It's important to have one of the key operators of the system be a doctor, along with a leading member of your staff."

• ***Don't skimp on training.*** "A key reason that a system which seems to be working well in many respects doesn't work out is that the staff and physicians have not had adequate training," notes Mr. Pinto. "It doesn't pay to skimp and go for the basic training module instead of having a trainer spend sufficient time onsite."

• ***Expect to add some new staff.*** "If you have 20 employees or more, you have to have one dedicated person who is constantly looking at the system, upgrading the system and doing everything possible to keep it functioning well," says Ms. Gyoerkoe. "That process is never finished."

Dealing with EHR Problems

Despite all of your best efforts, problems inevitably crop up. These strategies can help.

• ***Don't be discouraged by a temporary drop-off in patient volume.*** "Implementing an electronic system inevitably causes an initial slowdown in patient throughput and an accompanying drop in revenue," says Mr. Pinto. "That transient drop in revenue must be factored in when you're look-

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ing at the costs of getting the system in place and making the transition.

"It typically takes six months to a year in some settings to get back to one's accustomed volume of patients," he adds. "Although it varies from practice to practice, my clients typically report that one year after adoption they're between 90 and 110 percent of their former patient throughput. In other words, by then they've been able to see about as many patients as they did originally."

• ***Don't throw in the towel after six months without seeing how other practices have fared.*** "Let's assume you didn't do the site visits before purchasing your system," says Mr. Pinto. "Let's say you bought your system because the doctor liked it. Now it's several months post-install, and it's just not working out for you. Before you pack it up and send it back, you should visit at least two other users that are about your same practice size and have been using the system for at least a year. Observe them using it.

"Visiting those other users is just as valuable at this point as it is if you do it before you make the purchase," he notes. "If they're doing all right with the system, you'll have a better idea of whether or not your problems are solvable. Or, you may find that they're having problems too; maybe you'll discover that you're all among the first practices to adopt this system. If that turns out to be the case, you'll have to go to the vendor and try to resolve your concerns. If you can't work it out, you'll have to start over again with a new vendor that's more experienced."

• ***Not all trainers are created equal.*** "If you're having problems, it could be because you had the wrong trainer," Mr. Pinto says. "Keep in mind that whether your EHR vendor is large or small, the company is made up of professionals, some of whom are probably below average. So, make sure that you not only vet the company you go with, but that you vet the trainer they send you. If you're matched with Susan Smith, ask to talk to the office manager or lead doctor in a couple of practices that she's made the transition with recently. How was she? How much experience has she had?

"This is very much like picking an attorney," he adds. "You could choose to work with a famous law firm, but if you end up with a third-string attorney, it doesn't matter what name is on the door of the firm."

• ***Bringing back a trainer after six months can help make things go more smoothly.*** "When you're midstream, say four, six or eight months into the adoption process, it can make a lot of sense to either do another onsite visit to an adroit user of your system, or bring back a company trainer," says Mr. Pinto. "By this point, you've got the basic stuff down. Now you can get help moving to the next level and learn ways to get the most from your system."

• ***If you're switching systems, find a trainer who's helped others make that same transition.*** "If you're currently using Brand X and you're switching to Brand Y, ask to be matched with a trainer who has helped other practices make that transition," says Mr. Pinto. "This may not be possible in every situation, but it's possible in a great many of them."

• ***Keep in mind that vendors go through cycles.*** "This is true for all of these companies," says Mr. Pinto. "A company may get a reputation for being really great with customer service, and on the basis of that great reputation they get a lot of new customers. Then, they get overwhelmed with new installations and new problems to solve, and for a period of time their customer service goes down. So sometimes the thing that helped convince you to invest in a system isn't as great after you sign up."

• ***Don't change systems unless you really need to.*** "Don't decide to switch just because your system has some small inconveniences," advises Dr. Hageman. "The transition to a new system may be more difficult than you're expecting. Make sure you're changing for a good reason."

Making the Best of It

"If you have another 20 years to practice, you'd probably like this to be the last EHR system you buy for the rest of your career," notes Mr. Pinto. "In reality, the chances are good that you'll be changing systems, and maybe even vendors, before you retire."

Mr. Pinto points out that problems with EHR systems are not usually solely the result of a lack of effort on the part of the vendor. "In my experience, most of these companies realize that all ophthalmologists know all other ophthalmologists—it's a small, well-connected community," he says. "So they usually bend over backwards to make sure their customers are happy. But remember, these companies are made up of individuals with varying levels of skill and competence. If you're working with one individual and you're not getting satisfaction, it's perfectly appropriate to go higher up in the company and get matched with someone else.

"In the end, you have to go with the best company you can," he adds. "Take all of their advice regarding what's going to smooth adoption of the system, make sure that you get those critical site visits in, and make sure that you have doctor attentiveness to the process. This can't just be left to the lay staff; you have to have a doctor champion and leader. Then, follow your nose. Prepare yourself for a great deal of frustration and dysphoria for the first year that you're working with a new system. You're going to feel really dumb, and things will go really slow when you first start to use it. But if you follow the steps we've been discussing, odds are good that the system you've chosen will work out." REVIEW

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Cracking the Code of ICD-10

Walter Bethke, Managing Editor

ICD-10 uses a new format, terminology and codes. Here's what you need to know.

One of your patients comes to you with a corneal abrasion she got while on vacation. It seems she was posing for a photo when the exotic bird she was holding suddenly scratched her right eye. In 2013, using International Classification of Disease – 9th Edition coding, you would simply use the code for corneal abrasion. Starting October 1, 2014, however, your practice will have to select from the following ICD-10 codes: contusion of eyelid and periocular area (S00.1); unspecified injury of right eye and orbit (S05.91); abrasion of eyelid and periocular area (S00.21); abrasion of right eyelid and periocular area, initial encounter (S00.211A); struck by parrot (W61.02xA); struck by macaw (W61.12xA); struck by other psittacines (W61.22xA); or struck by duck (W61.62xA). Though apparently fantastical, the codes are real, and San Bernardino, Calif., consultant Kevin Corcoran, an expert on ophthalmic coding, uses this example when teaching his course on ICD-10, noting that it gives professionals a feel for what's coming. (Incidentally, S00.211A and W61.22xA are the correct answers.) "ICD-10 requires a lot more detail from the physician and the biller than they had to provide before," he says. It turns out this added detail is the tip of the iceberg when it comes to understanding ICD-10.

In this article, we'll take a look at how ICD-10 requirements are going to affect how you document a patient encounter, show how the new coding process differs from ICD-9 and decipher some of the new coding language for common ophthalmic patient presentations, so your practice can hit the ground running next October.

ICD-10 Overview

ICD-10 is a coding standard that emphasizes specificity in documenting a patient's visit, so much so that the codes in the new book number approximately 69,000. This is a big leap from the 14,000 codes used by ICD-9. "It stems from the fact that coding is going to be more granular and detailed," says Lisa Gallagher, vice president of technology solutions at the Healthcare Information and Management Systems Society, a non-profit group that seeks to improve health care through the use of computer systems. "With more information, we'll be able to perform better analytics in terms of the quality of care and population health. With ICD-10, the patient also gets an accurate diagnosis with accurate documentation that will lead to proper payment for the provider."

Mr. Corcoran says there are several

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key reasons why ICD-9 is on the way out. "First and foremost, it's a pretty old system," he says. "It's more than 30 years old. Also, some of the language and terms used in ICD-9 aren't used anymore—a good amount of medical practice has moved on in the past 30 years. Finally, ICD-9 doesn't offer enough detail."

As to why the extra details are important, Mr. Corcoran offers the following example. "Say an elderly lady, 80, comes into your office with a black eye, a bump on her head and decreased vision," he says. "She tells you that she was driving, noting she doesn't see too well anymore, and ran into the back of the car in front of her, causing her to hit her head on the steering wheel. Upon examination, you find she's now got traumatic cataracts that are hindering her ability to perform activities of daily living such as driving, and inform her that she needs surgery. In 2013, you would have looked at her cataracts, billed Medicare—probably using 366.16 (nuclear cataract)—and, since you didn't specify it was incidental to an auto accident, would get paid by the government health program. But in ICD-10, there is a code 'V43 (struck by automobile),' which would say to the payor, 'This was the result of a motor vehicle accident and therefore should be covered by auto insurance—not Medicare.' ICD-10 turns doctors into this great big reporting system, and third-party payors benefit from it.

"It's important to note that you can only code what's in the medical record," Mr. Corcoran continues. "With ICD-10, the medical record needs to be considerably more precise, and probably longer than it's been in the past, just to be able to code it. When Australia and New Zealand started implementing ICD-10 several years back, more than half of the charts weren't codeable. The reason was that, in order to use the ICD-10 coding system, physicians needed more precision in their descriptions. So, if a doctor simply writes, 'cataract,' it cannot be coded."

One of the unintended consequences of this hyper-specificity, and which may hit some physicians where they live, is that practices will no longer be able to use the so-called superbill after an exam, which some doctors use as a "cheat sheet" for the codes they need. There are simply too many possible codes to fit on a sheet of paper. "Right now, a superbill is not going to be provided [with ICD-10]," says Ms. Gallagher. "The set of codes in totality is too massive." A computer program may help doctors find the right codes—depending on how detailed their documentation is—but, at least in the initial period of ICD-10 adoption, a program may not give you all the codes. For this reason, ophthalmologists and practices who get to know the language of ICD-10, such as how it assigns ophthalmic codes to exam notes and the special terms it uses, will find they have a leg up when documenting their patient encounters and making sure their claims aren't rejected.

Inside ICD-10

It turns out that, in addition to understanding a new coding system, users of ICD-10 also need to know how to actually read the book, as it uses its own set of terms that may have different meanings than someone is used to. Here are tips for using the book and finding the right codes.

• ***Know the terms.*** "The terminology conventions used in the book influence how you use it," says Mr. Corcoran. "Unfortunately, you can't use the book like a ZIP code directory—you have to know how to read it."

One term used often in the book that has the potential to confuse a user is the word "excludes," since it has two meanings in the ICD-10 world. " 'Excludes' in simple English means to prevent from being a part of a group," says Mr. Corcoran. "However, in the ICD-10 book, it's used two ways: Excludes 1 and Excludes 2. In the book, the terms actually have very different meanings. Excludes 1 means two codes are incompatible and cannot be used together on a claim. For example, you'll notice that the code for blepharitis, H01.0, comes with 'Excludes 1: blepharoconjunctivitis,' meaning you can't code them both together.

"However, Excludes 2 is different," Mr. Corcoran continues. "It means that another code isn't included with the particular code you're looking at but it can coexist at the same time in the same patient. So the code for chalazion (H00.1) has the note 'Excludes 2: infected meibomian gland,' since it's possible for someone to have both conditions concurrently."

The word "and" also has an unexpected meaning in ICD-10; it means "and/or," which, unfortunately, is exactly the opposite of the generally understood meaning of the word. "So, if you just flipped open the book without bothering to learn its nomenclature and construction and made an assumption about what the word 'and' meant, you'd be wrong," says Mr. Corcoran.

ICD-10 also makes a point of specifying laterality in its codes, something that was absent in ICD-9. Here's how it codes laterality:

- 1 is the right eye;
- 2 is the left;
- 3 indicates bilaterality; and
- 9 means the side is unspecified.

For certain diagnoses, ICD-10 also requires that a seventh digit representing the severity of the condition be coded as well, most notably glaucoma:

- 1 represents mild disease;
- 2 is moderate;
- 3 is severe;
- 0 is unspecified; and
- 4 means it is indeterminate.

• ***Use all the chapters.*** The ICD-10 book has 21 chapters versus ICD-9's 17, and physicians have to be ready to use any of them for a given patient. "You can't just learn the eye chapter—

Chapter 7, with codes beginning with H—and throw away the others," says Mr. Corcoran. "For instance, if your patient has a diabetic eye condition you won't find it in the eye chapter. Instead, you'll find it in the chapter on the endocrine system, Chapter 4. The same with shingles; though shingles has ocular implications, if you looked in the eye chapter you wouldn't find it. You have to go to Chapter 12: Diseases of the Skin, to code ocular complications of shingles."

• ***Dig for GEMs.*** One of the aids the ICD-10 creators have provided for finding a proper code is known as General Equivalence Mapping files. These are software-based conversion tables that allow you to enter in an ICD-9 code and receive a general idea of the coding area in the ICD-10 manual where the appropriate new code or codes might be.

For instance, using the corneal abrasion example from earlier, entering the ICD-9 corneal abrasion code, 918.1, into a GEM converter would give you the ICD-10 code S05.00xA. Here, the letter "S" represents the chapter on injury or poisoning from external sources. You will then have to dig deeper in order to properly code the injury. So, in essence, the GEM will get you in the right neighborhood but you've still got to find the exact house. "Is the GEM a perfect match?" asks Mr. Corcoran. "Sadly, no. It's better than nothing, though, and will get you in the vicinity of the right answer." A good GEM converter can be found on the website of the American Academy of Professional Coders at http://www.aapc.com/icd-10/codes/.

Common Coding Examples

To help get a feel for some common diseases that crop up in the ophthalmologist's office, here are several examples provided by Mr. Corcoran that are among the many he covers in his ICD-10 training course:

ICD-10: Common Cataract Codes

Cortical age-related cataract, bilateral	H25.013
Age-related nuclear cataract, bilateral	H25.13
Combined forms of age-related cataract	H25.81
Anterior subcapsular polar age-related cataract	H25.03
Posterior subcapsular polar age-related cataract	H25.04
Congenital cataract	Q12.0
Cataract secondary to ocular disorders (degenerative) (inflammatory)	H26.22
Soemmering's Ring	H26.41
Other secondary cataract	H26.49
Pseudophakia	Z96.1
Dislocation of lens	H27.1

• ***Corneal ulcer.*** A patient presents with a central ulcer. In ICD-9 you'd note that it was a central ulcer, ignoring laterality, and use code 370.03. In ICD-10, however, you have these choices: H16.011 (central corneal ulcer, right eye); H16.012 (central corneal ulcer, left); H16.013 (central corneal ulcer, bilateral); and H16.019 (central corneal ulcer, unspecified).

• ***Cataract.*** When a patient is diagnosed with a nuclear cataract and the GEM file is used, it finds the ICD-10 code H25.819 (combined forms of age-related cataract, unspecified eye). "Might we probably know more than that about the patient?" muses Mr. Corcoran. "In terms of laterality, yes. But, now that we're in the ballpark, after looking at the actual section under H25.819, we see the real code will be H25.811, H25.812, or H25.813. It won't actually be H25.819 (unspecified)."

A practice may also see the occasional Flomax patient who needs me-

ICD-10: Common Glaucoma Codes

Open angle with borderline findings, low risk	H40.01
Open angle with borderline findings, high risk	H40.02
Anatomical narrow angle, primary angle closure suspect	H40.03
Ocular hypertension, bilateral	H40.053
Primary angle closure without glaucoma damage	H40.06
Unspecified open-angle glaucoma	H40.1 (plus a digit indicating severity)
Primary open-angle glaucoma	H40.11 (plus a digit indicating severity)
Low-tension glaucoma	H40.12 (plus a digit indicating severity)
Acute angle-closure glaucoma	H40.21
Pigmentary glaucoma	H40.13 (plus a digit indicating severity

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chanical dilation of the pupil during surgery. In the new coding standard, certain drugs have their own codes that need to be entered in the record for certain diagnoses. In this case, the coding would be H25.11 (age-related nuclear cataract, right eye), H21.81 (IFIS) and the code for the drug T44.6x5A (tamsulosin anti-adrenergic use).

• ***Diabetic eye disease.*** In some cases, ICD-10 creates just one code where ICD-9 used two, such as in the case of proliferative diabetic retinopathy. In ICD-9, the codes would be 250.52 (uncontrolled Type 2 diabetic with ophthalmic manifestations) and 362.02 (proliferative diabetic retinopathy). In ICD-10, however, you use one code for this patient: E11.359 (Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema).

Another new concept in ICD-10 is the need to note the patient's use of insulin with code Z79.4 (long term current use of insulin). "This is significant because the long-term use of insulin matters in public health," explains Mr. Corcoran. "If someone begins taking insulin early in life, they might be a big burden on the healthcare system for the rest of their lives."

• ***Glaucoma.*** Another example involves a patient who presents with uncontrolled, chronic open-angle glaucoma OU with severe visual field loss in the right eye and moderate field loss in the left. In ICD-9, the codes would be 365.11 (POAG, chronic simple glaucoma) and 365.73 (severe glaucoma).

In ICD-10, due to the widespread use of laterality, the proper codes would be H40.1113 (severe glaucoma, right eye), H40.1122 (moderate glaucoma, left eye) and the practice has the option of also including H53.40 (unspecified visual field defects) if it wanted to provide more information.

• ***Age-related macular degeneration.*** A patient you've been following for AMD presents with severe vision loss in her right eye. She admits to being a smoker. You find exudative AMD in the right eye and dry AMD in the left. You treat the right eye that day with an injection of bevacizumab.

To code this particular patient, you would use the codes H35.32 (exudative AMD), H35.31 (non-exudative AMD) and would also have to note Z72.0 (tobacco use). One thing to note is that there is no laterality when coding AMD.

Though ICD-10 will pose documentation, coding and technological challenges as practices overhaul their systems to accommodate the new system, one thing is clear: It won't be postponed and will be required for reimbursement come October 2014. "CMS informs us that we need to reinforce the message that the deadline is not going to change," says HIMSS' Ms. Gallagher. "It's come down from the secretary of the Department of Health and Human Services that it's not going to be delayed. They're sticking to the deadline." REVIEW

ICD-10: Common Cornea/External Disease Codes

Dry eye syndrome of bilateral lacrimal glands	H04.123
Epiphora	H04.2
Blepharitis	H01.0
Sjögren's syndrome	M35.02
Chalazion	H00.1
Entropion and trichiasis of eyelid	H02.0
Ptosis of eyelid	H02.4
Other chronic allergic conjunctivitis	H10.45
Mucopurulent conjunctivitis	H10.0
Central corneal ulcer	H16.01
Keratoconjunctivitis sicca, not specified as Sjögren's	H16.22
Keratoconus	H18.6

ICD-10: Common Retina Codes

Retinal detachment with retinal break	H33.0
Serous retinal detachment	H33.2
Horseshoe tear of retina without detachment	H33.31
Central retinal artery occlusions	H34.2
Central retinal vein occlusion	H34.81
Retinopathy of prematurity	H35.1
Type 2 diabetes mellitus with unspecified diabetic retinopathy	E11.31
Type 2 diabetes mellitus with proliferative diabetic retinopathy	E11.34
Non-exudative age-related macular degeneration	H35.31
Exudative age-related macular degeneration	H35.32
Drusen (degenerative) of macula	H35.36
Puckering of macula	H35.37

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A Brave New World Awaits Ophthalmology

Robert M. Kershner, MD, MS, FACS, Palm Beach Gardens, Fla.

An ode to innovation that suggests the future is bright in eye care.

My work as a consultant to the pharmaceutical and medical device industries provides me with a unique perspective on emerging technologies. Looking back over the past two decades at the significant advances that have occurred in drug development, lasers and surgical technology made me wonder about what lies ahead. It might surprise you to know that researchers worldwide have been quietly working away at deciphering the genomics and molecular pathways of the human cell; this will radically challenge how we think about and treat the most common ophthalmic diseases. From the front to the back of the eye, and everything in between, the future of our profession is about to change.

My essay here could not, and does not attempt to, be all-inclusive of every technology and advance on ophthalmology's horizon. Here are some of the ones I find intriguing.

Cataract

It is probably not necessary to review the data on one of the most intriguing emerging technologies in ophthalmology, namely the femtosecond laser, to place it in its proper perspective. The device, which has been used successfully in excimer laser refractive surgery to create the corneal flap, has crossed over to cataract surgery. The high costs associated with its adoption (upwards of $600,000 for the laser including its annual service contract and supplies) limits its availability to all but the largest of practices or surgical centers. Combined with the inability to recoup the costs through reimbursement, limited experience and a paucity of studies proving efficacy (Does it really perform the steps of cataract surgery better or as well as an inexpensive set of disposable instruments?) Despite this, almost a third of cataract procedures may have been performed with this laser to make the corneal incision, open the lens capsule and fragment the crystalline lens. There is a big push by the major players to advance this technology, leaving little doubt that it will change the way we perform cataract surgery in the future. The latest selling points for the technology, according to manufacturers' claims, include: Bausch + Lomb's Victus curvilinear corneal docking system; LensAR's precise three-dimensional measurement of intraocular lens tilt/decentration and lens-cutting protocols to reduce the ultrasound energy required for lens fragmentation; and Alcon's LenSx laser's improved visualization that uses its computer's image-

This article has no commercial sponsorship.

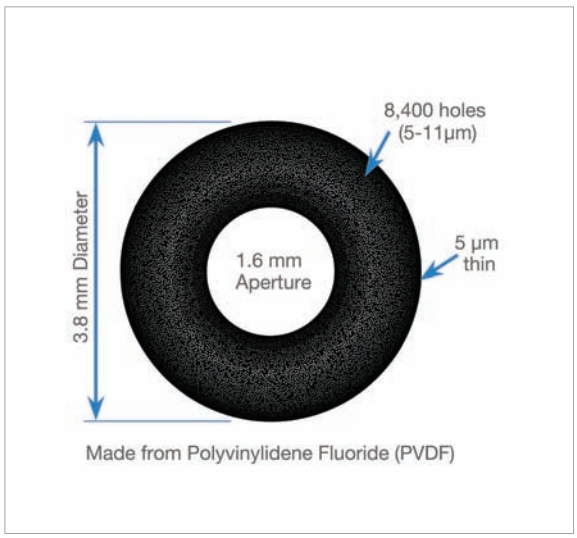
guided system. Abbott Medical Optics recently acquired OptiMedica's Catalys which features a patient docking Liquid Optics interface guidance system that provides a clear optical path for the OCT and laser. What is missing from all of these devices is the ability to emulsify, extract the lens and replace it with an IOL. When we see that module, rapid adoption will surely follow.

One of the important additions to the refractive cataract procedure is the ability to measure, in real time, the refractive aberrations of the eye at the time of cataract surgery. The WaveTec VerifEye for the ORA System provides intraoperative wavefront aberrometry that potentially could improve patients' refractive outcomes. As more and more patients demand clear, uncorrected acuity following surgery, this technology may yet find a role that would encourage its widespread adoption.

New intraocular lenses that correct refractive error, ocular aberrations and presbyopia are on the horizon, and many of the lenses already in the pipeline are finally receiving Food and Drug Administration approval. Recent approvals include the AcrySof Toric IOL, Tecnis Toric 1-Piece IOLand Trulign Toric IOL. The real advances in IOL design would of course offer the patient a truly accommodative lens. The hurdles from a design and regulatory standpoint of developing an IOL "cure" for presbyopia are not inconsequential; nonetheless the search for the holy grail continues.

Elenza is a next-generation, electronic accommodating IOL that is designed to provide a complete visual range, from near, intermediate and distance, what its maker calls an "AutoFocal" lens. This electro-active IOL uses an integrated circuit and a micro-sized power-cell with an expected 50-plus year rechargeable life, to create smart optics; and a proprietary combination of liquid-crystal chemistry, that in milliseconds automatically adjusts focusing power electronically to maintain constant in-focus vision. Sounds pretty neat to me, but what digital device today is just as good in five years? Have they thought about obsolescence? And if the battery still works in five years, what happens if the electronics fail?

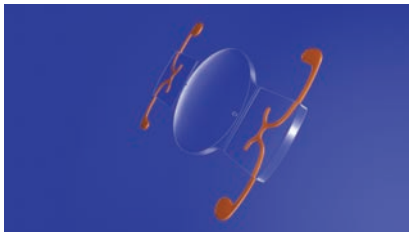
Perhaps the establishment of the Medical Device Innovation Consortium (mdic.org), with its unique partnership between the FDA and private enterprise, may make some headway in developing regulatory protocols that will streamline the time it takes to bring a medical device to the public. With few of the major players yet to get onboard, only time will tell whether or not this noble effort succeeds. Stay tuned.



The Kamra from AcuFocus is one of three inlay technologies aimed at presbyopia correction.

Cornea

If IOLs do not solve the problem of presbyopic correction, perhaps inlays will. ReVision Optics intracorneal Raindrop near vision inlay is a microscopic hydrogel lens for the correction of presbyopia that, after implantation under a femtosecond laser-created flap, creates a prolate-shaped cornea. The AcuFocus Kamra Intracorneal inlay uses a pinhole to provide uncorrected near vision. Remember when they sold those as glasses? Likewise the Presbia Flexivue Microlens, implanted under a femtosecond-created flap using Presbia's proprietary insertion tool.


The Trulign Toric is one of a handful of new intraocular lenses making recent debuts.

One of the greatest advances in the treatment of keratoconus and ectatic corneas has been the application of riboflavin, or vitamin B2, combined with excitation by a 370-nm wavelength of ultraviolet-A light. When activated by UV-A light, riboflavin (from the reduced form of the sugar, ribose, combined with its yellow oxidized "flavin") creates new bonds between adjacent collagen strands within the corneal stroma (cross-linking). Avedro's KXL System for accelerated corneal crosslinking, uses its investigational LASIK Xtra integrated illumination system to apply the appropriate amount of UV-A following the creation of a corneal flap and application of riboflavin. All we need now is to get the FDA to agree to this treatment modality.

What advances can we expect in the diagnosis of corneal infections? Most clinicians believe that they can adequately tell the difference between a bacterial and a viral keratoconjunctivitis just by looking. They may be sadly mistaken. More than 90 percent of all conjunctivitis is treated with an-

tibiotics, yet more than half may be viral in origin. The AdenoPlus, RPS rapid diagnostic detector is accurate in more than 89 percent of cases and is quick and easy to use. Stop guessing, and just do the test.

Glaucoma

New approaches we are seeing in the treatment of glaucoma, which include both new drugs and surgical devices, are rooted in a new understanding of how glaucoma ultimately damages retinal ganglion cells. Significant strides are being made in the neuroprotection of RGCs. Here is a little background and a look at some of the more interesting approaches.

Apoptosis is programmed cell death. It can be initiated by both an extrinsic pathway, which includes a number of apoptosis-inducing ligands, or by intrinsic pathways that are activated after the loss of pro-survival signals from neighboring retinal, optic nerve or brain neurons. Downstream regulation of extrinsic and intrinsic pathways of apoptosis initiators are becoming interesting and viable targets for glaucoma therapies. Nitric oxide (NO) is an important messenger in intra- and extracellular communication. NO is formed from L-arginine by nitric oxide synthase (NOS). NOS is well-distributed in the trabecular membrane. This molecule is implicated in vasodilatation, trabecular membrane contractility, neurotransmission, neurotoxicity, inflammation and anti-apoptosis of RGCs (neuroprotection).

RGC-targeted glaucoma treatments now in clinical trials include medications injected into the eye that deliver survival and growth factors to RGCs, also useful for stroke and Alzheimer's disease, such as cytidine-5-diphosphocholine; and the adenosine agonist CHA, which has been shown to significantly increase conventional outflow facility. Mechanical approaches such as electrical stimulation of RGCs delivered via tiny electrodes implanted in contact lenses or other external devices are also under investigation. Memantine, an NMDA glutamate receptor antagonist that blocks glutamate excitotoxicity, is the first drug approved for use as a neuroprotective agent in moderate to severe Alzheimer's dementia. Evidence of its usefulness in glaucoma is mounting as we elucidate protective effects against RGC loss. Human trials of stem cell therapies are also in the planning stages.

Evidence of the usefulness of memantine in glaucoma is mounting as we elucidate protective effects against retinal ganglion cell loss.

Drugs such as brimonidine, which activate alpha-2 adrenoreceptors, first showed promise as a neuroprotective, but recent data suggests otherwise. Caspase inhibition increases retinal cell survival, and a siRNA-based caspase inhibitor is now in human testing in a multicenter trial for non-arteritic ischemic optic neuropathy.

We all know that the optic nerve, being derived from CNS neurons and covered with CNS myelin, does not regenerate. Glial cells release inhibitory molecules that actively signal RGC axons to stop growing. A number of these molecules have been identified and drugs are being developed to overcome their inhibitory influences. For example, antibodies to the oligodendrocyte-derived protein Nogo are in clinical trials for spinal cord injury, and neurotrophins are a promising class of drugs that have been tested in ALS, Parkinson's and other neurodegenerative diseases. It is only a matter of time before these advances translate into ways to protect the optic nerve, prevent its degeneration and encourage its regeneration.

Measuring Intraocular Pressure

Intraocular pressure is still one of the pillars of glaucoma management, and better ways of measuring IOP are being developed. Implandata has created a 24-hour intraocular pressure measurement device that offers continuous telemetric measurement of intraocular pressure. The system consists of an implantable micro sensor, which does the pressure sensing, and an external handheld device, which measures and stores the data and transfers energy to the micro sensor telemetrically. The Sensimed Triggerfish Sensor is a soft hydrophilic single-use contact lens, which contains passive and active strain gauges embedded in the silicone to monitor fluctuations in diameter of the corneo-scleral junction. The output signal is sent wirelessly from an antennae that is placed around the eye and connected to a portable recorder through a thin flexible data cable.

The patient wears the device for up to 24 hours; the data is then transferred from the recorder to the practitioner's computer via Bluetooth technology for immediate analysis. The data collected is said to directly correlate with fluctuations in intraocular pressure. Bye, bye Dr. Goldmann.

Surgeons have revisited the surgical approach to glaucoma. Recognizing that the trabecular meshwork and its juxtacanalicular connections to Schlemm's canal are the site of much of the resistance to outflow, new microinvasive glaucoma surgical technologies and improved surgical techniques are being developed to take advantage

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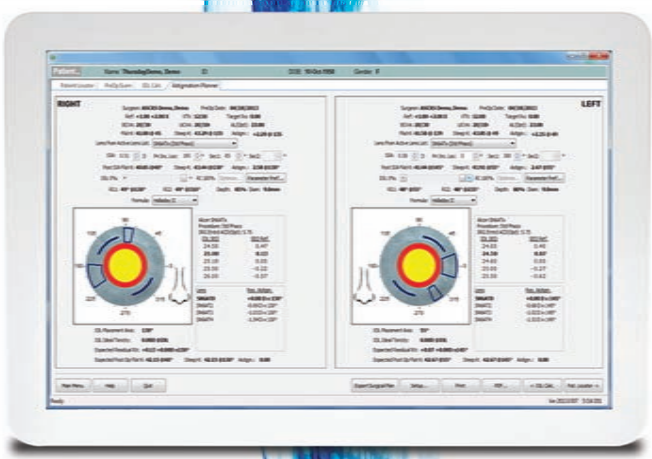

Pre-op

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Intra-op

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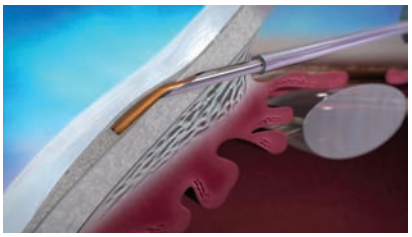

The XEN Gel Stent creates a diffuse outflow of aqueous from the anterior chamber into the non-dissected tissue of the subconjunctival space.

of this approach. The Glaukos iStent Trabecular Micro-Bypass is said by its manufacturer to be the first MIGS device to create a permanent opening in the trabecular meshwork (which seems like old news to me); it can be implanted during cataract surgery and is the smallest medical device ever approved by the FDA.

The Ivantis Hydrus Microstent is claimed to be the world's first "intracanalicular scaffold" for the treatment of primary open angle glaucoma. The Hydrus procedure is said to be less invasive than traditional glaucoma surgery, and can be performed during cataract surgery through the same incision. Roughly the size of an eyelash, the Hydrus Microstent is made from a super-elastic, biocompatible alloy (Nitinol) that has been used in other implantable devices.

Another player exploiting the MIGS approach to glaucoma surgery is Rheon Medical, a start-up affiliated with the Ecole Polytechnique Fédérale de Lausanne. Its EPFL-designed implantable device is considered a "microtap." Containing a magnetic disk surrounded by a silicon tube, it is designed to rotate around an eccentric axis that compresses the tube, to either a greater or lesser extent. In this way the flow rate through the tube can be adjusted remotely.

AqueSys XEN Gel Stent, which is about the width of a human hair and smaller than the eye of a needle, is made of a permanent, soft, collagen-derived gelatin. Upon implantation, it creates a diffuse outflow of aqueous from the anterior chamber into the non-dissected tissue of the subconjunctival space.

InnFocus-Innovia, the company that created an orbital tissue expander for microphthalmia and anophthalmia, is developing the MIDI-Arrow Glaucoma Device drainage implant. This device consists of a microtube made from SIBS (polystyrene-block-isobutylene-block-tyrene) polyester that is inserted into the anterior chamber of the eye. In one version, the tube shunts fluid into a bleb made in the conjunctiva. In another version, the tube is attached to a plate that receives the shunted fluid while also maintaining the bleb. The third round of clinical trials is already under way.

Retina—AMD

Patients with age-related macular degeneration were told not that long ago that there was nothing that could be done for their disease, and that they could expect to lose vision or go blind. Today, these patients have hope. Advances in the treatment of retinal diseases have occurred at a breathtaking pace. We have witnessed game-changing recombinant antibodies targeting vascular endothelial growth factor, originally used to treat various cancers, being turned on the blinding retinal diseases. The incredible results that we have witnessed in our patients with the use of these molecules are going to be tough acts to follow. However, the landscape is about to change.

Biosimilars and Biosuperiors

The first generation of recombinant antibodies targeting VEGF, that included Macugen (pegaptanib sodium injection), has been largely replaced by the more efficacious Lucentis (ranibizumab). The humanized antibody fragment Lucentis, marketed by Novartis and Roche/Genentech, generated sales of $3.67 billion in the United States in 2011. The full-length therapeutic antibody Avastin recorded sales of $5.6 billion. These are not

IMPORTANT SAFETY INFORMATION FOR THE VERION™ REFERENCE UNIT AND VERION™ DIGITAL MARKER

CAUTION: Federal (USA) law restricts this device to sale by, or on the order of, a physician.

INTENDED USES: The VERION™ Reference Unit is a preoperative measurement device that captures and utilizes a high-resolution reference image of a patient's eye in order to determine the radii and corneal curvature of steep and flat axes, limbal position and diameter, pupil position and diameter, and corneal reflex position. In addition, the VERION™ Reference Unit provides preoperative surgical planning functions that utilize the reference image and preoperative measurements to assist with planning cataract surgical procedures, including the number and location of incisions and the appropriate intraocular lens using existing formulas. The VERION™ Reference Unit also supports the export of the high-resolution reference image, preoperative measurement data, and surgical plans for use with the VERION™ Digital Marker and other compatible devices through the use of a USB memory stick.

The VERION™ Digital Marker links to compatible surgical microscopes to display concurrently the reference and microscope images, allowing the surgeon to account for lateral and rotational eye movements. In addition, the planned capsulorhexis position and radius, IOL positioning, and implantation axis from the VERION™ Reference Unit surgical plan can be overlaid on a computer screen or the physician's microscope view.

CONTRAINDICATIONS: The following conditions may affect the accuracy of surgical plans prepared with the VERION™ Reference Unit: a pseudophakic eye, eye fixation problems, a non-intact cornea, or an irregular cornea. In addition, patients should refrain from wearing contact lenses during the reference measurement as this may interfere with the accuracy of the measurements.

Only trained personnel familiar with the process of IOL power calculation and astigmatism correction planning should use the VERION™ Reference Unit. Poor quality or inadequate biometer measurements will affect the accuracy of surgical plans prepared with the VERION™ Reference Unit.

The following contraindications may affect the proper functioning of the VERION™ Digital Marker: changes in a patient's eye between preoperative measurement and surgery, an irregular elliptic limbus (e.g., due to eye fixation during surgery, and bleeding or bloated conjunctiva due to anesthesia). In addition, the use of eye drops that constrict sclera vessels before or during surgery should be avoided.

WARNINGS: Only properly trained personnel should operate the VERION™ Reference Unit and VERION™ Digital Marker.

Only use the provided medical power supplies and data communication cable. The power supplies for the VERION™ Reference Unit and the VERION™ Digital Marker must be uninterruptible. Do not use these devices in combination with an extension cord. Do not cover any of the component devices while turned on.

Only use a VERION™ USB stick to transfer data. The VERION™ USB stick should only be connected to the VERION™ Reference Unit, the VERION™ Digital Marker, and other compatible devices. Do not disconnect the VERION™ USB stick from the VERION™ Reference Unit during shutdown of the system.

The VERION™ Reference Unit uses infrared light. Unless necessary, medical personnel and patients should avoid direct eye exposure to the emitted or reflected beam.

PRECAUTIONS: To ensure the accuracy of VERION™ Reference Unit measurements, device calibration and the reference measurement should be conducted in dimmed ambient light conditions. Only use the VERION™ Digital Marker in conjunction with compatible surgical microscopes.

ATTENTION: Refer to the user manuals for the VERION™ Reference Unit and the VERION™ Digital Marker for a complete description of proper use and maintenance of these devices, as well as a complete list of contraindications, warnings and precautions.

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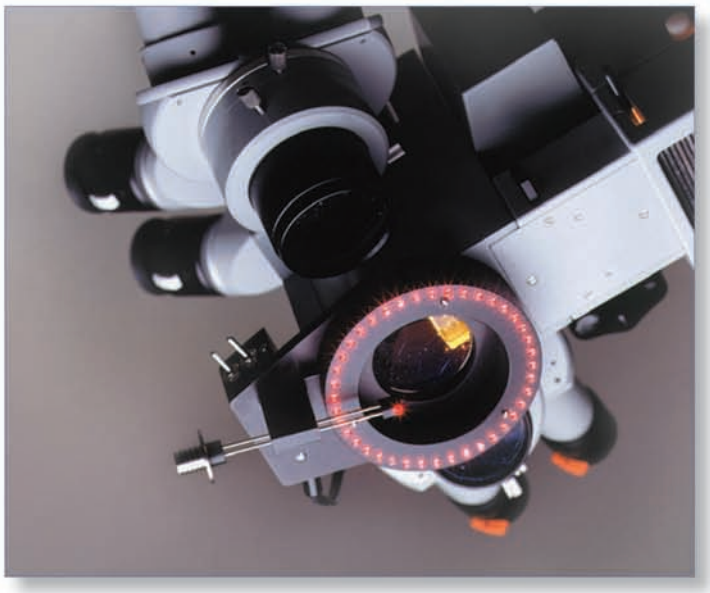

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insignificant drugs. Approved indications for Lucentis include wet AMD, diabetic macular edema and macular edema following central retinal vein occlusion. Patents covering Avastin and Lucentis are going to expire over the next several years. Get ready to witness a nor'easter blowing that will irrevocably change the landscape and pave the way for biosimilar antibodies. The first Avastin biosimilars are already in clinical trials and there are at least 10 others in the pipeline undergoing further development.

What about biosuperiors? The next generation of anti-VEGF antibodies is led by the fusion protein aflibercept, marketed under the name Eylea, which is administered intravitreally every month for three months followed by dosing every eight weeks for two months. Eylea is also indicated for the treatment of patients with macular edema due to CRVO. Another new treatment is Jetrea (ocriplasmin), an intravitreal injection, proteolytic enzyme, which for the first time allows a retinal surgeon a non-surgical alternative to relieve vitreomacular adhesion.

Anti-amyloid therapy, which has already been used clinically in Alzheimer's disease, has been shown to protect against retinal pigmented epithelium damage and vision loss in an animal model of AMD.

AMD is characterized by the accumulation of extracellular lipid- and protein-containing deposits between the RPE and Bruch's membrane. These sub-RPE deposits contain activated components of the complement system (such as C3b and C5b-9), which boost the host defense against invading pathogens. In addition, amyloid P component and proteins such as complement factor H, vitronectin, clusterin/apolipoprotein J, apolipoprotein E (apoE), and amyloid-β (Aβ) have been shown to be involved in the immune and inflammatory responses.

Comparing unique anti-Aβ antibodies, which target the two most common forms of Aβ (i.e., Aβ40 and Aβ42), has shown promise in preserving retinal function and protecting the RPE. Clinical use of anti-Aβ antibodies may have therapeutic value in the treatment of both early and advanced stages of AMD.

Another intriguing set of molecules is the miRNAs (or miRs), which are small, noncoding RNAs that negatively regulate gene expression post-transcriptionally. These molecules play an important role in pathological angiogenesis and oxidative stress, and they trigger the inflammatory and immune responses associated with AMD. Presently there are several miRNAs whose direct involvement in choroidal neovascularization and RPE atrophy has been well-established, and this makes them tempting therapeutics for the treatment of AMD.

Retina—Diabetes

Available interventions for diabetic retinopathy and diabetic macular edema include laser photocoagulation therapy and vitrectomy. Unfortunately, these oft-used therapies primarily target the advanced stages of disease. The biochemical pathways that result in the vascular occlusion and fragility that are the hallmarks of DR have been elucidated. Several biochemical mechanisms—including protein kinase C-β activation, increased VEGF production, oxidative stress, accumulation of intracellular sorbitol and accumulation of advanced glycosylation end products—have been targeted for pharmaceutical intervention. The new goal is to intervene in DR and DME earlier in the disease and provide prophylaxis prior to the development of the neovascular and sight-threatening stages.

Advanced laser systems that facilitate precise treatments for DR include the new OD-OS Navilas Laser System, which incorporates OCT imaging, planning and treatment capabilities in one device. Sounds like a winner to me.

Retinopathy of Prematurity

Many have thought that retinopathy of prematurity was a conquered disease. With more premature babies surviving than ever before, the need for interventions is just as great as in the 1950s. Almost 95 percent of infants born at 23 weeks of gestation, and 40 percent of all infants born prior to 32 weeks suffer from severe multisystem complications. We have recently learned that the driving force in normal fetal development, that is missing in prematurity, is sufficient production of growth factors. Insulin-like growth factor I (IGF-I) has been shown to be associated with several of the most serious complications, namely, ROP, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis and impaired brain growth. Prema-

Oraya Therapeutics' Stereotactic Radiotherapy delivers X-ray therapy through the sclera, as in this illustration.

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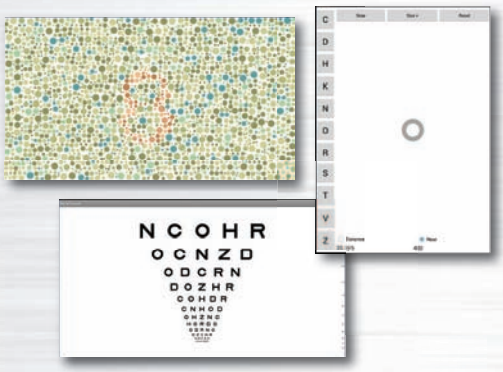

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cure, a pharmaceutical company based in Uppsala, Sweden, has been working to commercialize an Insulin-Like Growth Factor 1 (IGF-I) with or without its natural binding protein, IGFBP-3, which has been shown to prevent the complications of preterm birth. (Premacure was recently acquired by Shire, PLC, which is continuing the Phase II study of protein replacement therapy.)

Retina—Devices

Quantel Medical, a manufacturer of diagnostic ultrasonic devices, released its new ultrasonic probes for A and B scans recently and has received FDA approval for its Vitra Multispot laser, which provides advanced pattern-scanning technology for retinal treatments.

Clarity Medical Systems, manufacturer of the RetCam3, a retinal imaging device with its integrated optical systems, is said to enhance the clinician's ability to diagnose, manage and treat retinal diseases.

Oraya Therapeutics uses highly targeted, low-voltage X-rays to inhibit and prevent the growth of choroidal neovascularization associated with wet AMD. Oraya Therapy Stereotactic Radiotherapy is considered a first-line treatment designed to maintain or improve vision while reducing the required number of intravitreal anti-VEGF injections.

Recently released two-year data from the INTREPID study confirmed a 25 percent mean reduction in anti-VEGF injections over two years in a broadly inclusive cohort of non-naïve wet AMD. Patients identified in the first year of the study as ideal response candidates maintained an impressive 45 percent mean reduction in anti-VEGF injections through the two-year visit, with superior vision to the non-treated group.

TODDD, the Topical Ophthalmic Drug Delivery Device, releases drugs over several months. It rests on the sclera, concealed under the upper or lower lid. While it has no optical power, it incorporates contact lens design elements for comfort and stability.

Drug-Delivery Systems

One of the major challenges facing ophthalmologists in the treatment of glaucoma is the ability to deliver glaucoma drugs consistently and uniformly into the anterior segment where they are needed. Patient compliance is the most common issue, as well as the need to overcome pharmacologic constraints. The bioavailability of drugs delivered topically is quite poor; only 5 percent or less actually makes it into the eye with topical delivery. Though long the preferred method of drug delivery, primarily because there haven't been many other options, we are now recognizing that it is mostly ineffective. The eye has several barriers—corneal, blood aqueous and blood vitreous—that additionally make drug penetration inefficient. Sustained drug delivery has been successful for up to six months with intravitreal implants such as Vitrasert, and up to three years with Retisert and Iluvien. There are, however, no available systems for long-term drug delivery to the anterior segment of the eye. Studies presently under way include the use of mucoadhesives, viscous polymer vehicles, transporter-targeted prodrugs, and receptor-targeted functionalized nanoparticles. Older methods are being revisited for use in the eye, including iontophoresis, the lowly punctal plug and contact lens delivery systems. A few of these might be useful in treating diseases affecting the back of the eye as well.

Contact Lens

Lets take a look at the low-tech contact lens. Hydrogels, when saturated with a drug, colloidal nanoparticles or molecular imprinting, can be easily manufactured, placed on the eye, removed and replaced as necessary. The challenges of lens migration, insufficient oxygenation of the cornea, foreign body and risk of infection cannot be overlooked, however.

Amorphex Therapeutics has developed its own Topical Ophthalmic Drug Delivery Device, which is reminiscent of the old Ocusert (pilocarpine ophthalmic). Using its proprietary knowledge of polymer formulations, the company has successfully incorporated a wide variety of drugs into its polymer metrics: prostaglandins; timolol; prednisolone; dexamethasone; brimonidine; and ibuprofen. *In vitro* drug release studies confirm the ability of these polymers to create consistent drug-release profiles over many months. Simply slip this piece of plastic under the patient's upper eyelid, and she can forget about her drops. Sounds easy, doesn't it?

If you can't get the drug onto the eye, maybe you can stop the drug from getting off of the eye. That concept is the basis for the use of punctal plugs as drug delivery systems. QLT Inc. has developed its proprietary punctal-plug drug delivery technology that potentially could deliver a controlled and sustained release of a variety of drugs to the eye through the tear film. The punctal plug, impregnated with the medication to be delivered and placed into the eyelid punctum, could be retained for the desired treatment

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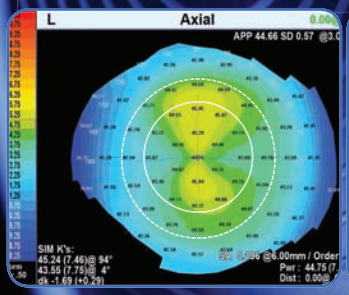

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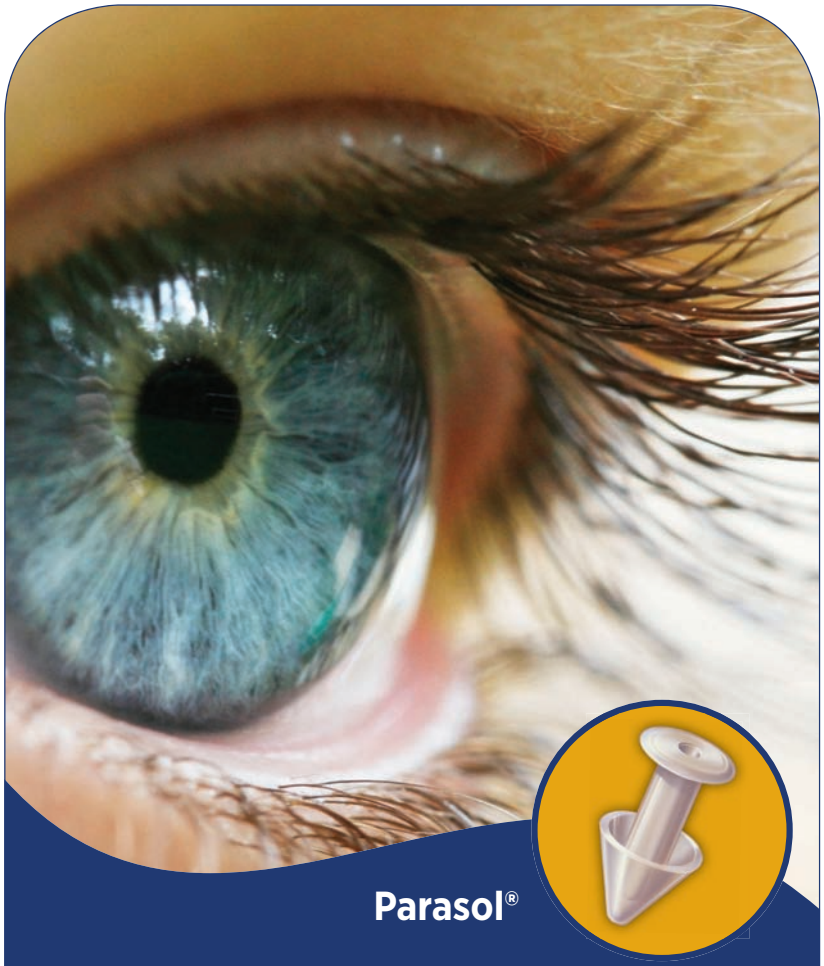

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duration and removed or replaced as necessary.

If these methods have enough spark to excite your interest, then perhaps the EyeGate II Delivery System, a method of delivering corticosteroids using iontophoretic treatment, might. Iontophoresis is the method by which an inert electrode electrolyzes water to produce hydroxide or hydronium ions. These ions can be used to propel charged molecules, such as steroids, through tissues. The method has demonstrated efficacy in its Phase III study where topical multiple daily dosing with prednisolone was compared to once-weekly treatments with the device. The endpoints were equally met in both groups.

Neurotech boasts an intriguing Encapsulated Cell Technology implant system, which continuously delivers recombinant biotherapeutics for up to two years. This technology uses an immortalized and transformed RPE cell line, which can secrete all modern classes of biotheraputics: cytokines; monoclonal antibodies; antibody Fabs; single chain Fv; and other scaffolds at a rate of 50 pgm/cell/day. The device is made of a semi-permeable polysulphone exterior capsule and internal scaffold of polyethyleneteraphtalate yarn. The cells grow within the hollow capsule, and when implanted in the vitreous, allow for drug diffusion through the pores in the capsule, which can be engineered to release specific amounts.

Novel Therapeutics

Shedding light on the biochemical pathways that signal transcription has been furthered by a new understanding of the regulatory roles of small molecules that turn genes on and off. With each new discovery of a pathway, such as the cytokines that trigger inflammation, comes a new potential drug target. Because these

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pathways are universal to human cells, targeting drugs which may be useful in diseases such as rheumatoid arthritis and polycythemia vera may also have topical applications for dry eye.

Kinases are enzymes whose primary job is to transfer phosphate groups from ATP (remember that molecule as the "currency" of the cell's metabolic fuel requirements?) to a five- or six-carbon sugar, protein or lipid. Phosphorylation, well known for some time for its role in glycolysis, also plays an important role in turning pathways on and off. To date, hundreds of molecules targeting a specific kinase are undergoing investigation for their potential to treat disparate diseases, from solid tumors to atopy. A complete discussion of this topic is well beyond the scope of this article, but a few, novel therapeutics deserve mentioning.

Dry-Eye Therapies

Human tear film fluid is composed of a complex mixture of proteins, glycoproteins, lipids and small molecules. Several tear biomolecules have been shown to be excellent biomarkers for autoimmune diseases and infections, and as such could be useful for diagnostics.

It is difficult to analyze tears; after all, we only produce microliters of the precious liquid. The time and expense required to analyze a sample with ELISA testing, or by using a laboratory with expensive automated devices, precludes routine use. Rapid, highly reproducible assays for tear proteins, tear osmolarity and tear molecules could be of benefit in making a quick diagnosis. TearLab Diagnostics has FDA approval to market its osmolarity tester as an accurate biomarker to assess the extent of dry-eye disease. The desktop handheld device is easy to use, fast and accurate, and needs only 50 nanoliters of tears to assess tear film osmolarity. Hyperosmolarity is a known marker for dry eye; a difference between the two eyes is also supportive in making the diagnosis. Measuring other molecules in tears such as lactoferrin, which is a tear-specific protein that is reduced in keratoconjunctivitis sicca, may be beneficial when making a diagnosis.

Physicians must get involved, provide industry with direction, and feed the incubators with new discovery.

One of the more intriguing new drugs for dry eye is one that is presently in Phase III testing. SARcode Bioscience (Shire) is evaluating the safety of a topically applied 5% solution of Lifitegrast. Lifitegrast is a first-in-class molecule that inhibits T-cell inflammation by blocking the binding of 2 key cellular surface proteins (LFA-1 and ICAM-1). These receptors mediate the chronic inflammatory cascade triggered by T-lymphocytes (CD3). These cells carry the LFA-1 receptor on their surface, which binds to ICAM-1, which in turn initiates the cytokine cascade. Lifitegrast, by blocking the binding to the receptors, prevents T-cell migration into tissues and arrests the trigger for inflammation.

Thoughts for the Future

Medical innovation is alive and well. Supported by generous investment and funding, the right research team, and perhaps a big cash payoff if the drug or device hits, can be just the medicine needed to stimulate development of the next generation of therapeutics. Who better to direct and lead the pursuit of these miracles than the physicians who will use them to treat patients? To succeed, research and development must include physician-led innovation. Patients don't drive technology, doctors do. This concept, of which I am a strong proponent, was recently supported in a Viewpoint article published in the March 20, 2013 issue of the *Journal of the American Medical Association*.

If necessity is the mother of invention, then adversity is the mother of innovation. Every time a physician gets frustrated with the inability to treat a patient, the seed for a solution is planted. Traditional academic research may not be the best vehicle to test new devices and drugs. It is difficult to adequately assess, in randomized control trials, the independent impact of an innovation on patient care. The physician who will use the treatment is in the best position to determine efficacy. Let's face it, our history is awash in physician-led discoveries: looking at a shard of plastic and deciding it could be made into an intraocular lens implant, or figuring out how an ultrasonic device used to clean teeth might be used to remove a cataract.

Physicians must get involved, provide industry with direction, and feed the incubators with new discovery. When that day arrives, our patients will enter an in-office technology suite, and in less than a blink of the eye, have their crystalline lens removed, refractive correction applied, and a custom laser-lathed IOL inserted to restore perfect vision at any distance, with a physician viewing the whole thing on a computer screen. Just dreaming. REVIEW

Dr. Kershner is a physician innovator, president and CEO of Eye Laser Consulting and a professor and chairman of the Department of Ophthalmic Medical Technology at Palm Beach State College.

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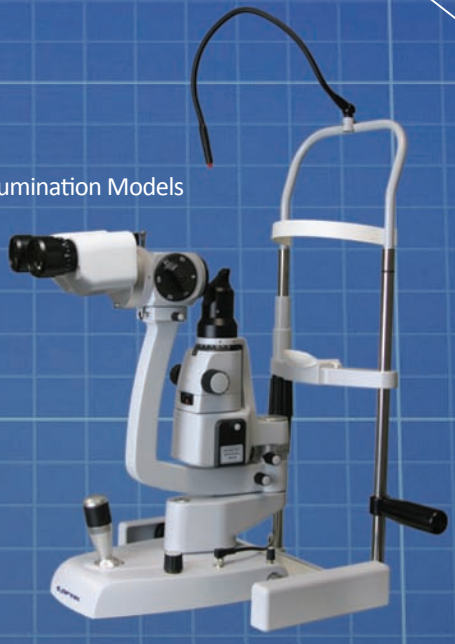

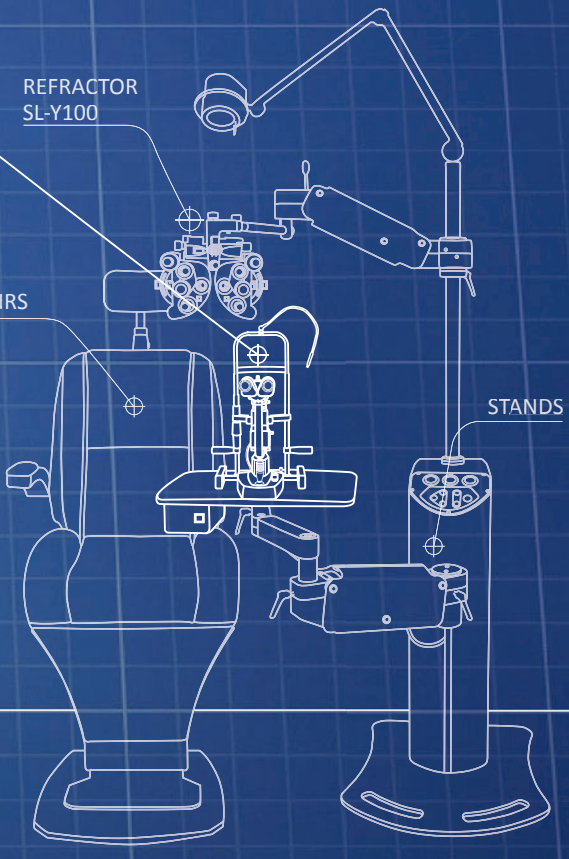

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The FDA's Struggle For Redemption

Frank Celia, Contributing Editor

The embattled agency seeks to reinvent itself. Will budget cuts derail the effort before it gathers steam?

Managing chronic pain is one of health care's most enduring problems. Certain patient populations—for example, those with severe rheumatoid arthritis—wake up every morning to levels of pain equivalent to those caused by the blunt force trauma of a serious automobile crash. Without pharmaceutical help, it is impossible for such patients in some cases even to rise from their beds.

Though opiates remain the mainstay short-term pain reliever, to avoid drug dependency among patients with long-term or lifetime conditions, physicians usually turn to NSAIDs. The severity and pathogenesis of NSAID gastrointestinal side effects were not fully understood until the discovery of prostaglandins in the late 20th century. By 1998, one study could conclude NSAID-related GI events produced a higher death rate than cervical cancer, asthma or malignant melanoma.[1]

So pharmaceutical manufacturers began experimenting with NSAID derivatives that would produce fewer GI side effects. Against this clinical backdrop, the Vioxx scandal ran its course.

It is impossible to understand the FDA's current efforts to improve its public image, change its internal workings and mend its relationship with industry without acknowledging the profound impact on the agency and society as a whole caused by the Vioxx scandal and the era it embodied: Within days of Merck's September 30, 2004 withdrawal of the NSAID amid charges of its doubling the incidence of serious cardiovascular events, a public outcry erupted, led by surgeons and lawmakers. "I am concerned whether FDA has been sufficiently aggressive in monitoring drug safety," said one Congressman at the time. On the *New England Journal of Medicine* website, a prominent cardiovascular surgeon wrote: "The senior executives at Merck and the leadership at the FDA share responsibility for not having taken appropriate action and not recognizing that they are accountable to the public health."

Critics put the death toll at a minimum of 55,000. Congress investigated, as the lay press offered up portrayals of a Food and Drug Administration in cahoots with the industry it regulates. Within a year, Merck's CEO had stepped down, soon followed by the FDA commissioner, who departed under a cloud of additional accusations, including deliberate delay of the "morning after" pill. In 2006, he pled guilty to criminal charges stemming from financial holdings in companies under FDA purview during his reign. His replacement managed to last until the end of George W. Bush's presi-

This article has no commercial sponsorship.

dency, but not before enduring calls for his own resignation following the agency's allegedly botched response to safety problems with the antibiotic Ketek (telithromycin), the blood thinner heparin, the cholesterol drug Vytorin (ezetimibe and simvastatin), the diabetes drug Avandia (rosiglitazone), and the spinach *Salmonella* outbreak of 2008.

Faced with an ongoing series of controversies, the FDA, perhaps understandably, closed ranks. An increased focus on safety at the expense of innovation marked the period of 2007 to 2011, according to agency critics. Approval times lengthened, red tape proliferated, FDA scientists grew remote and uncommunicative. Turnarounds that once took 30 days now took six months or a year. Review deadlines passed by unmet and without explanation. Meanwhile, healthcare innovations increasingly debuted in Europe rather than the United States. To this day, drug and device manufacturers continue to express frustration and bewilderment.

Though the agency disputes these gripes in their particulars, in public statements its leaders tacitly acknowledge the need for fence-mending. Speaking at an NEHI conference last year, FDA Commissioner Margaret A. Hamburg, a 2009 appointee, conceded, "For the people here from the medical product side—those who develop new devices, diagnostics, and drugs—these have not been easy times," then added this olive branch: "The FDA must not be a roadblock. Just the opposite: Our job is to enable innovation." Other high-ranking agency officials have voiced similar comments.[2]

Recognizing the discord, Congress passed laws last year aimed at streamlining and modernizing the FDA. Unfortunately, recent mandatory federal budget cuts triggered by the sequestration will almost certainly jeopardize these efforts *(See Less Money, More Problems, page 85)*, yet another stumbling block confronting this institution's anything-but-surefooted entry into the 21st century.

Current Incarnation

Vioxx is far from the first public disaster to drive government policy. On the contrary, the FDA owes its very existence to a litany of pandemic health debacles. Three stand-outs include: In the 1930s, the 73 deaths linked to "Dr. Massengill's Elixir Sulfanilimide" persuaded Congress to grant the agency its fundamental function of evaluating the safety of new drugs before they go on the market, which it had not previously possessed. Before the widespread harm caused by birth-control intrauterine devices inspired the federal Device Amendments of 1976, the agency had little control over medical devices. Finally, the FDA's current incarnation owes a great deal to the emergence 25 years ago of the AIDS virus.

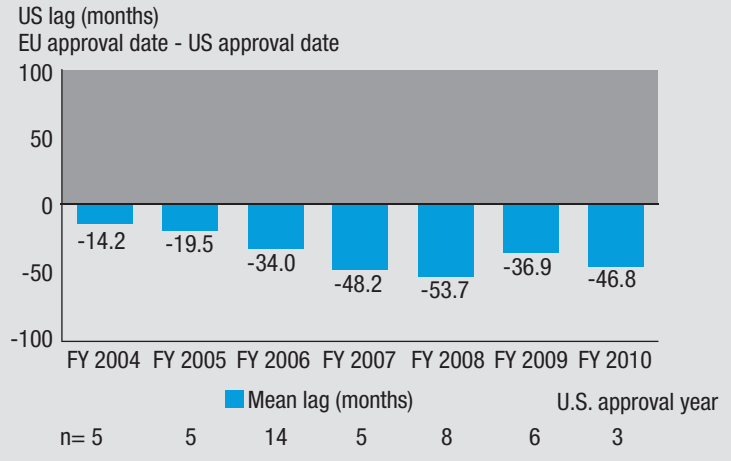
By the 1980s, a new drug application took an average of two and a half years to be acted upon, and some took as long as seven or eight. "Drug lag," a catchphrase of the era, resulted in 70 percent of new therapies first gaining approval overseas, and 60 percent available elsewhere for more than a year before being approved in the United States.[3]

When the AIDS epidemic occurred, the wasting, swiftly moving, infectious disease put enormous pressure on the agency to speed up its drug-approval process.[4] Lawmakers, industry and patient activists all came together to figure out a way to finance the streamlining of clinical trials. What they came up with was the Prescription Drug User Fee Act (PDUFA) of 1992. This law paid for additional FDA drug review staffers by charging pharmaceutical companies a fee for every new drug application. In exchange for this extra financial support, the FDA committed for the first time to adhere to review deadlines. In 1994, for example, PDUFA required the FDA to review and act upon 55 percent of new drug applications within 12 months. Designed to be evaluated and renewed every five years, PDUFA is now in its fifth iteration.

Despite sporadic criticism that industry's funding of FDA constituted a conflict of interest, PDUFA has been considered a success. By all accounts, application times shrunk significantly in the 15 years following its passage. Encouraged by PDUFA, the medical device industry and Congress agreed to a similar law called the Medical Device User Fee and Modernization Act (MDUFMA) of 2002, which also established user fees and agency deadlines.

Matters proceeded harmoniously until the renewal of PDUFA IV and MDUFMA II in 2007, which, following Vioxx and other problems, granted the FDA broad new powers. For

Figure 1. Mean U.S. PMA Devices Approval Delay



Note: Represents original PMAs
Source: Data compiled from all PMAs approved in the United States for 12 different medical device companies, where total sample size n=46; BCG analysis.

example, PDUFA IV imposed more stringent conflict-of-interest rules on physician advisory committees. But, since most physician experts in any given field often have ties to the field's drug manufacturers, even assembling a committee now requires an excessive amount of time, industry argues. Additionally, something called Risk Evaluation and Mitigation Strategies (REMS), a PDUFA IV tool designed to codify manufacturers' post-approval safety evaluations and thus shift burden and risk away from the pre-approval process, has been widely labeled a failure. According to one industry white paper, REMS have had the opposite of their intended effect: "Negotiating with the Agency on REMS requirements has stretched review times and lengthened FDA's review processes."[5]

Much as when in 1992 industry and the FDA came together to negotiate the terms of PDUFA, the two did so again last year to hash out PDUFA V, MDUFMA III, and a companion law called the FDA Safety and Innovation Act (FDASIA) of 2012.

Provisions of the new laws include:

• ***Accelerated review times.*** Experimental drugs aimed at treating serious or life-threatening diseases can gain "breakthrough therapy" status, and thereby earn the right to be judged by surrogate endpoints that could bring it to market faster. For the device industry, the FDA committed to the goal of issuing decisions on 91 percent of 510(k) submissions within 90 days.

• ***Enhanced communication and transparency.*** A plan for better relations between the FDA and biopharmaceutical companies calls for "additional review clock time for the agency to meet with applicants during the review as well as to address activities that occur late in the review cycle for these highly complex applications," according to an FDA commitment letter.

• ***New risk calculator.*** To replace the agency's traditional *ad hoc* decision making process, the FDA agreed to develop a codified framework for weighing risks against benefits during human drug and biologic reviews. The law calls for the framework to be consistent and systematic, and give greater consideration to the perspectives of patients who are to receive the drug. In February the FDA unveiled a draft document for its proposed risk calculating framework. Following industry input, a final draft is expected next year.

• ***Patient-focused drug development.*** The agency agreed to a program that would gather patient perspectives on the severity of their condition, their unmet medical needs and their willingness to bear the risk of potential side effects. The law calls for 20 nationwide, patient-focused meetings to occur over the next five years. The first meeting, held in April, canvassed the concerns of patients with chronic fatigue syndrome and myalgic encephalomyelitis. Other topics for meetings scheduled for this year include HIV, lung cancer and narcolepsy.

• ***Higher User Fees.*** With each PDUFA and MDUFMA renewal, user fees have risen, and this round proved no exception. Last year drug companies paid an estimated $1 billion in fees, and device companies paid about $90 million (if you count the Mammography Quality Standards Act), or about 25 percent of the agency's total spending. Factoring in fees collected from tobacco companies, food manufactures, etc., user fees account for about 40 percent of FDA revenue.

Strained Relationship

In the run-up to the most recent federal legislation, the health-care manufacturing industry and its lobbyists unleashed an onslaught of position papers laying out their argument against the FDA. One of the most comprehensive and eloquent emerged from the California Healthcare Institute, a biomedical industry organization. A sample from its introduction by CHI President David Gollaher, PhD, encapsulates industry's universal theme: "The Agency-industry partnership is strained by unexplained regulatory delays, by a lack of clear standards for what clinical data are necessary for product approval, and by a bureaucracy whose communications are neither consistent nor predictable."[5]

Since 2007, agency performance has slipped, according to some calculations. Drug and biological review times have increased 28 percent, device 510(k) clearances have slowed by 43

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Indications and Usage

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

Important Risk Information about LOTEMAX® GEL

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

Please see brief summary of full prescribing information on adjacent page.

References: 1. LOTEMAX GEL Prescribing Information, September 2012. **2.** Fong R, Leitritz M, Siou-Mermet R, Erb T. Loteprednol etabonate gel 0.5% for postoperative pain and inflammation after cataract surgery: results of a multicenter trial. *Clin Ophthalmol.* 2012;6:1113-1124. **3.** Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. *J Pharm Bioallied Sci.* 2011;3(1):89-100. **4.** Data on file, Bausch & Lomb Incorporated. **5.** Coffey MJ, Davio SR. Viscoelastic and sedimentation characterization of loteprednol etabonate ophthalmic gel, 0.5%. Poster presented at: Association for Research in Vision and Ophthalmology (ARVO); May 6-10, 2012; Fort Lauderdale, FL. Poster #6283/D1143. **6.** Lotemax Prescribing Information, April 2006. **7.** Rajpal RK, Roel I, Siou-Mermet R, Erb T. Efficacy and safety of loteprednol etabonate 0.5% gel in the treatment of ocular inflammation and pain after cataract surgery. *J Cataract Refract Surg.* 2013;39:158-167.

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INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

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

Bacterial Infections

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

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

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

PATIENT COUNSELING INFORMATION

Administration

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

Risk of Contamination

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

Contact Lens Wear

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

Risk of Secondary Infection

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

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percent and pre-market device reviews (i.e., for those not deemed substantially equivalent to existing products) are taking 75 percent longer. [5]

Additionally, the United States now faces increased regulatory competition from overseas, particularly the European Union, whose 27 member states now form the world's largest healthcare market. For complex medical devices evaluated by the FDA's premarket approval process, the EU has consistently offered a faster route to market. But in recent years the delay has grown longer still, with products being approved in Europe nearly four years ahead of the United States, up from just over a year ahead in 2004 *(See Figure 1).*

Between 2007 and 2011, the number of drugs approved in the EU first has risen significantly, as well, pharmaceutical firms contend. "Recent years show some evidence of a new 'drug lag' with products approved on average two and half months earlier in the EU than in the United States."[5] *(See Figure 2.)* The resulting loss of business harms more than just U.S. employment and corporate profits. "There is no substitute for tinkering with an invention in the real world," observes the CHI paper. "Over time, this process builds the chain of experience essential to technological innovation. Thus an American company's decision to launch a novel device in Germany because the regulatory pathway there is faster and more predictable, results in German surgeons and technicians learning the fine points of applying the technology first. And, of course, it also means that German patients benefit from U.S. innovation before Americans do."[5]

Although industry trade organizations signed off on the various provisions of the new laws last year, whatever positive effect they may have will take time to be realized. Large swaths of the legislation—the new risk calculator stipulation, for example—remain works-in-progress not yet implemented.

When not tight-lipped, the rank and file admit to limited expectations. "I don't know whether things are changing," says Eric Buckland, PhD, CEO of Bioptigen, manufacturer of specialized OCT scanners. "I know that Jeff Shuren [director of CDRH] has said he is turning over a new leaf. He has said publicly and privately that the FDA is going to be faster and more responsive. But what we don't know is the impact of the budget sequester. Will they have the time to make these things happen? Will they have the staff?"

A Lightning Rod

While industry makes a compelling argument, it is by no means the only point of view. The FDA has long been "a lightning rod for strong criticism from across the political and ideological spectrum," according to a *JAMA* editorial.[6] Like a lenticular print, the agen-

Less Money, More Problems

In the summer of 2011, as a condition for voting to raise the federal debt ceiling, Congressional Republicans insisted on a plan to reduce the deficit. So a bipartisan "super-committee" was assembled to recommend budget cuts. To motivate the super-committee, legislation was drawn up that would trigger automatic, across-the-board spending reductions if it failed to make more specific suggestions—the so called "budget sequester."

When the super-committee came up empty-handed, the sequester went into effect this March, slashing roughly $100 billion a year over the next decade from both defense and domestic spending.

The FDA lost $209 million from its 2013 fiscal year—$126 million from its budget and another $83 million in user fees. Total agency spending amounts to about $4 billion per year.

The belt-tightening comes at a difficult time for the FDA, as it is in the process of making agency-wide improvements mandated by federal laws passed last year such as PDUFA V, MDUFA III and the FDA Safety and Innovation Act. Furthermore, drug and device manufacturers who agreed to higher user fees—that is, monies companies pay when they file a new drug application or open a factory, and annual rates on existing products—in exchange for more predictable timetables, greater transparency and an improved model for calculating risk vs. benefit from the FDA, now have to stand by while much of that extra cash goes unspent.

"Although we will continue to collect these fees, they will remain on deposit in the U.S. Treasury," FDA Commissioner Margaret Hamburg told the audience at the Food and Drug Law Institute's annual conference earlier this year. "They cannot be used to support critical tasks such as issuing regulations and guidances, keeping up with inspections, and delivering on performance commitments to speed the pathway to approval for many of the products Americans depend on."

User-fee seizures particularly rankle drug manufacturers, who last year signed off on a PDUFA V formula that over five years would increase pharmaceutical user fees by a total of $100 million. (Drug companies paid about $1 billion in fees last year.)

"These prescription drug user fees cannot, by law, be used for any purpose other than to support FDA's human drug review program," according to a statement issued by the Pharmaceutical Research and Manufacturers of America. "Their sequestration does not decrease the nation's deficit, but only serves to exacerbate the severe budgetary constraints of a historically underfunded agency. This is detrimental to patients, regulatory science and public health."

Many worry the sequester's 5-percent budget setback will cause the FDA to fall short of its agreed upon, legislated goals—and not without good reason. At the agency's Science Board Advisory Committee meeting in February, Chief Scientist Jesse L. Goodman, MD, informed attendees that decreased funding would very likely shrink services: "It's thought it will generally slow some of the review times overall and certainly reduce some of the more costly things we have to do, such as inspections, particularly foreign inspections of facilities."[1] —*F.C.*

1. Science Board to the Food and Drug Administration Advisory Committee Meeting, held on February 27, 2013, FDA's White Oak Campus. Transcript available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM347951.pdf. Accessed Sept. 11, 2013

cy's appearance changes depending upon the angle from which it is viewed. To offer just one example, many blame the review deadlines imposed during the PDUFA era for higher rates of post-market safety problems.

A study published last year in the *American Journal of Political Science* examined a dataset of FDA drug approvals for decision timing and quality. It found that limiting review times induced "a piling of decisions before deadlines, and these 'just-before deadline' approvals are linked with higher rates of post-market safety problems (market withdraws, severe safety warnings, safety alerts)."[7]

On the device side, a 2011 report issued by the Institute of Medicine, an independent non-profit organization, concluded that the 510(k) process, used to evaluate devices that are substantially equivalent to those already functioning in the marketplace, should be scrapped and replaced. "Rather than continuing to modify the 35-year-old 510(k) process," the paper states, "the FDA's finite resources would be better invested in developing an integrated premarket and post-market regulatory framework that provides a reasonable assurance of safety and effectiveness throughout the device life cycle."[8]

Industry itself has expressed frustration with the 510(k) process, saying it has become too burdensome and time-consuming. Some companies have suggested the United States follow the lead of the European Medicines Agency, the regulatory body of the EU market, which differentiates its moderate-risk devices into two tiers, higher risk and lower risk. Such a system might forestall the kind of incongruities often found in the United States, where relatively non-invasive products like OCT scanners are grouped in the same category as hip replacement joints.

Science or Theater?

FDA reviewers and advisory committees have always taken into consideration the views of patient populations and the severity of the conditions to which a drug or device is targeted. For instance, it can be widely agreed upon that pregnant women experiencing nausea and patients with a particularly deadly form of cancer will have wildly divergent tolerances for potential treatment risks, and regulators might act accordingly. What the agency has lacked until now is a systematic, ongoing program for gathering and assessing such patient perspectives, especially for conditions where conclusions might be less *prima facie* obvious.

Thus the model legislated by PDUFA's Patient Focused Drug Development provision offers a fresh paradigm for public health and is receiving a great deal of attention from patient advocacy groups, industry and the agency itself. According to draft documents, it will serve as an important information source for whatever new risk calculation framework the FDA eventually develops: "FDA recognizes that patients have a unique and valuable perspective on these considerations [benefit-risk assessment] and believes that drug development and FDA's review process could benefit from a more systematic and expansive approach to obtaining the patient perspective."

But here too, when looked at from a different angle, questions emerge. Are patients really the best judges of what

Outreach to Ophthalmology: IOLs and Databases

Making a greater effort to incorporate the opinions of medical professionals into its approval protocols has been a key objective of recent Food and Drug Administration modernization reforms. To this end, ophthalmology has participated in two joint FDA workshops thus far, one with the American Glaucoma Society and another with the American Academy of Ophthalmology.

The most recent, held at FDA headquarters on Oct. 11 and organized by the AAO, gathered clinicians, academics, federal employees and industry experts with the goal of improving the regulatory science surrounding premium intraocular lenses. Participants focused on endpoint methodologies to be used in evaluating IOL safety and effectiveness.

"The idea is to figure out a way to better assess performance of these lenses," says Thomas Oetting, MD, professor of clinical ophthalmology at the University of Iowa College of Medicine and a workshop moderator. "I think there is a feeling both on the part of the eye surgeons and from the perspective of the FDA that the existing IOLs on the market have performed OK so far, but there's room for improvement. If we can find better ways to assess the performance of these lenses before they're approved, they might become more popular, and in the end our patients will be happier."

Issues discussed at the meeting included subjective and objective methods for measuring lens performance; what established safety and performance endpoints should be modified and how to proceed in doing so; and identifying areas in which more validated, standardized patient-reported outcome measures might be needed.

A similar joint workshop, co-sponsored by the AGS, occurred in October 2012, and was considered a success. That meeting focused on the construction and reliability of normative databases in the field of glaucoma imaging.

Ophthalmologists can expect more such partnerships in the coming years, according to FDA officials. "Our mission includes not only responsibility to protect the public health but also to promote the public heath," Deputy Director of the CDRH William H. Maisel, MD, said at the AGS workshop, "and that latter aspect is something we've really been focused on over the last two or three years."

Getting safe and effective devices to market in a timely manner is the FDA's new motivation, he said. "We recognize we can't do this alone, and in many respects, being here today is emblematic of that. We really feel we need to understand the science, engage with the clinical community, industry, the patient community, so that we can find the sweet spot, if you will, and really advance the field." —*F.C.*

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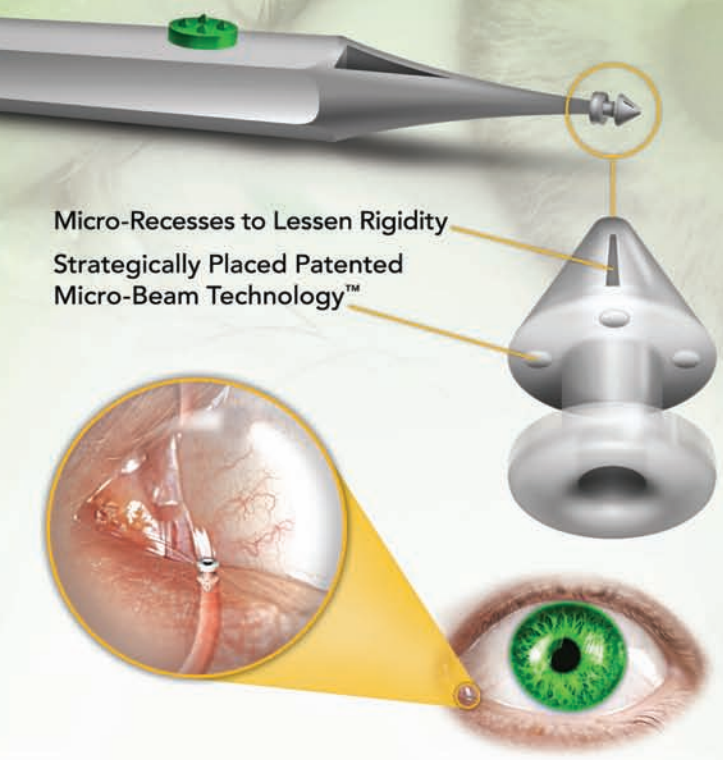

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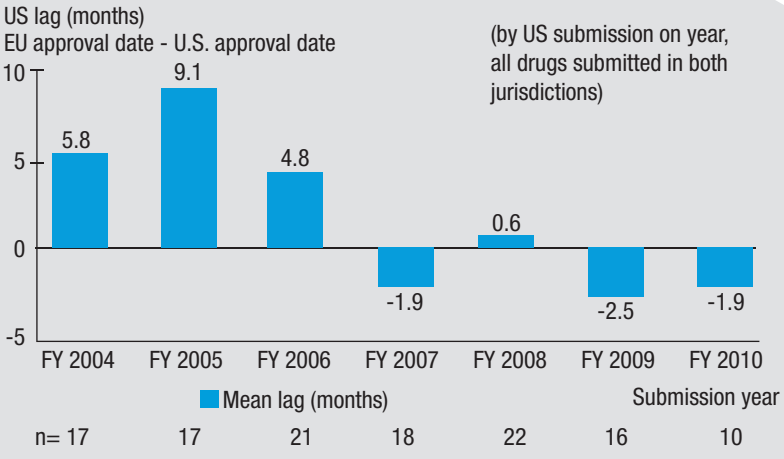
Figure 2. Mean U.S. New Drug Approval Delay



Note: Sample comprises only drugs being reviewed in both the United States and the European Union, data are categorized by U.S. submission year. Where drug has not been approved in one jurisdiction delay is counted as difference between first approval and 1/23/2011. Difference between 2004 and 2006 and 2007 and 2009 found to be statistically significant at the 5 percent significance level. Source: FDA drug database; EMAdrug database; BCG analysis.

therapies they should receive, or even what risks they are willing to bear? The most fiercely dedicated patient advocates sometimes change their minds when serious side effects materialize. One AIDS advocate, looking back on PDUFA's drug approval acceleration, lamented: "We have arrived in hell … AIDS activists and government regulators have worked together, with the best intentions, over the years to speed access to drugs. What we have done, however, is to unleash drugs with well-documented toxicities onto the market, without obtaining rigorous data on their clinical efficacy."[7]

There is also the question of whether the Patient Focused Drug Development program in its current state represents the most scientific means of collecting data. "I find the outreach effort rather poorly thought through," remarks Daniel Carpenter, PhD, a professor of government at Harvard University who has studied the FDA and other regulatory bodies. "It risks substituting theater for science. A more scientific approach would be to commission anthropologists, psychologists and sociologists to conduct surveys, experiments and ethnographies to get a better sense of patient risk and benefit perception. Instead, the FDA is inviting people to come to meetings, ensuring that the population will not be a representative one. The public meeting strategy will select for a population that is likely to tell the FDA a message that is different from that of the average patient. The power of placebo effects alone could tilt the subsample of participants toward those with a favorable benefit-risk profile for new treatments."

An added concern is that the meetings invite the participation of drug companies, Dr. Carpenter adds. "This is a red flag. One might ask why treatment specialists, i.e., doctors, are not included," he says. "If the FDA's concern is that patients would be afraid to speak truthfully with doctors in the room, do they honestly believe that having drug company representatives in the room is not going to shape what patients tell them?"

Quantitative vs. Qualitative

Another new mandate closely watched by the health-care world will be the development of a benefit-risk template for agency decision-making. In the draft document outlining its proposed framework, the FDA acknowledged that in the two years of negotiations leading up to PDUFA V, industry made it clear it would have preferred a more quantitative model, such as the "semi-quantitative" framework developed by PhRMA's Benefit-Risk Assessment Team, which has been used by the private sector for several years. However, such an approach, the FDA argued, would "require assigning numerical weights to benefit and risk considerations in a process involving numerous judgments that are at best debatable and at worst arbitrary."

The FDA document continues: "The subjective judgments and assumptions that would inevitably be embodied in such a quantitative decision modeling would be much less transparent, if not obscured, to those who wish to understand a regulator's thinking."

Describing its own proposed framework as a more "qualitative descriptive approach," the FDA did still acknowledge that many components of any scientific risk-benefit assessment would, by necessity, be quantitative.

The FDA's proposal consists of a simple spreadsheet with five key decision factors running down the left side:

1. Analysis of Condition—describes the severity of the disease.
2. Current Treatment Options—describes what treatments exist.
3. Benefit—results of the clinical trial and the implications of the primary and secondary endpoints.
4. Risk—the adequacy of the safety database, clinical pharmacology, etc.
5. Risk Management—what can be done to mitigate safety concerns.

These five decision factors are judged by two subjective criteria, listed along the top row of the chart:

1. Evidence and Uncertainties—unknowns and how they could affect risk and benefits.
2. Conclusions and Reasons—describes the implications of the facts, as the reviewers see them.

Finally, in the bottom row of the

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framework, the reviewers include their Benefit-Risk Summary Assessment, a succinct, well-reasoned summary that clearly explains the rationale for whatever regulatory action is taken.

In May, PhRMA issued a written response to this model. Among its main concerns appears to be the question of how much input and access the reviewed drug's sponsor would have to the chart during its assembly: "While PhRMA understands that one of the primary uses of the framework will be to facilitate internal decision-making within the agency, PhRMA encourages the FDA to consider what information sponsors can provide to support FDA's assessment of benefit-risk, either in marketing applications, during review, or in post-marketing safety reports." The letter then adds: "PhRMA would like to understand if sponsors will have the opportunity to review the FDA's benefit-risk framework for their products before the assessment is posted."

Vioxx Revisited

At their core, the FDA's responsibilities entail weighing potential risks against potential benefits of new drugs and devices. A look at the past quarter century reveals the essential dilemma confronting the agency to be a Janus-faced one, perhaps insolubly so: If the FDA focuses on protecting against risk and review times slow down, it finds itself criticized for jeopardizing the public's health. If it errs of the side of benefits and review times accelerate, it finds itself accused of the very same thing.

Its mission would be difficult enough if it only required predicting the future. But the agency cannot even benefit from an agreed-upon, retrospective assessment of its past. As a case in point, a second look at the Vioxx recall proves instructive. Does Vioxx really deserve to be called, in the words of one Congressional testimony, the "single greatest drug safety catastrophe in the history of this country or the history of the world"?

For starters, studies published after public attention moved on raise significant questions about the 55,000-deaths estimate. Although Vioxx and other COX-2 inhibitors (like Bextra, which was pulled from the market in 2005) present some increased risk of cardiovascular events, it has been found to be no higher than that posed by other NSAIDs.[9] Furthermore, the one factor distinguishing COX-2 inhibitors from other NSAIDs, their GI protective qualities, has been greatly missed by practitioners. Rates of GI events serious enough to require hospitalization rose 21 percent among NSAID users in the years following the recalls, according to a study presented at the 2007 annual meeting of the American College of Rheumatology.[10] Many physicians question whether the cardiovascular health gains achieved by removing Vioxx and Bextra from the market have now been outweighed by a surge in serious gastrointestinal events.

While Merck certainly tried to minimize the drug's negative side effects, it did nothing more untoward than any other drug firm does when marketing a product, according to Ted Frank, an attorney and adjunct fellow at the Manhattan Institute's Center for Legal Policy, who followed and wrote weblog posts about the Vioxx litigation, which eventually resulted in a $4.85 billion settlement in 2007. "There were Merck executives who were taking Vioxx," he notes. "Merck's corporate officers were not hovering over this drug cackling and tensing their fingers. This is a drug they thought worked and they thought was safe." It also bears mention that, despite extensive investigation, criminal charges were never filed against Merck or any of its employees.

None of this is meant as an apologia for Merck, nor any corporate malfeasance it may have committed, nor the FDA's role in any wrongdoing, but merely to illustrate that if the Vioxx imbroglio itself, the locus of so much angst and turmoil in health care and society at large, cannot be clearly characterized, even at a decade's remove, we can better appreciate the difficulties that lie ahead for the FDA.

In the final analysis, the questions presented by FDA's reform efforts are the same ones that arise whenever health care and limited public resources overlap: How much funding should the safeguarding of public health receive? How much say should patients have in the treatments they undergo? At what point do the needs of the many supersede the needs of the few, and vice versa?

Every society must answer such questions for itself, sometimes more than once a generation. If the FDA's current reformation throws light on their resolution or brings more transparency and visual acuity to the terms of their public debate, then at least a portion of its genuine but uncertain promise might be fulfilled. REVIEW

Mr. Celia is a freelance health-care writer based in the Philadelphia area.

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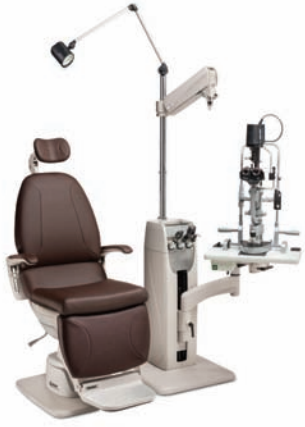

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Dry AMD: Focus on Protecting the RPE

Reduction or maintenance of geographic atrophy lesion size in the retinal pigment epithelium has garnered increased attention.

Maria E. Maldonado, Charles C. Wykoff, MD, and David M. Brown, MD, Houston

Age-related macular degeneration is a complex, multifactorial disease characterized by the degeneration of photoreceptors and retinal pigment epithelial cells with or without choroidal neovascularization. While significant progress has been made in the treatment of the exudative or wet form of AMD characterized by CNV, no therapy has been approved for the treatment of the nonexudative or dry form of AMD, which accounts for 85 percent of all AMD cases.[1]

While the exact causes of AMD remain unclear, factors such as aging, oxidative stress, light damage and genes are all known to play a significant role.

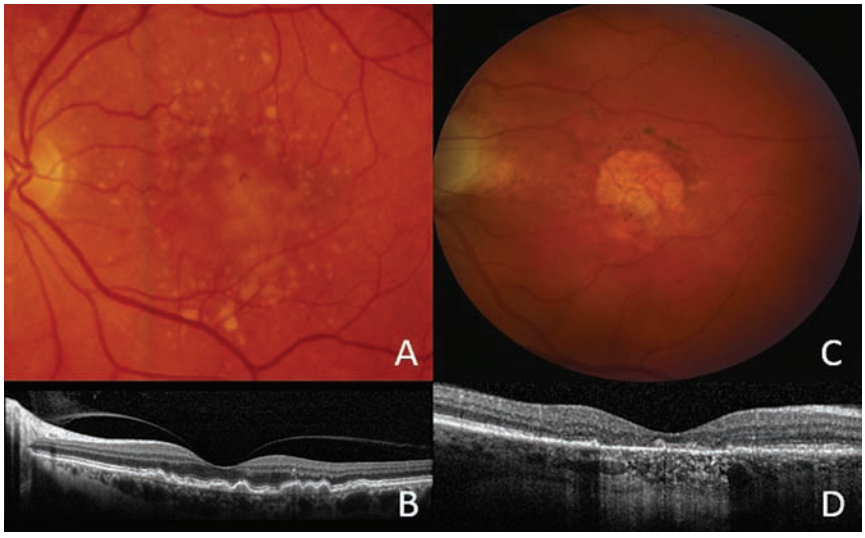

Figure 1. Progression of age-related macular degeneration showing: A) Early stages of AMD with drusen and RPE pigmentary changes on fundus photography; B) Early stages of AMD with drusen visible on optical coherence tomography; C) Late stages of AMD with geographic atrophy with surrounding drusen and RPE pigment clumping; and D) Late stages of AMD showing GA on OCT.

Clinical manifestations of early AMD include the appearance of extracellular deposits of drusen between Bruch's membrane and the RPE, visible clumps of pigment in the macula, and subretinal deposits of oxidized proteins and lipids (lipofuscin) within the RPE. For nonexudative AMD patients, RPE dysfunction progresses to RPE cell damage and death, potentially leading to regions of geographic atrophy *(See Figure 1)*, scotopic sensitivity and photoreceptor cell death.[2,3] Geographic atrophy and the accompanying retinal changes of dry AMD account for approximately 20 to 25 percent of severe visual loss and for a much larger portion of moderate visual loss in AMD patients.[4,5]

Recent biological and histological findings have supported an association between rod photoreceptor cells and nonexudative AMD. Symptoms of nonexudative AMD such as parafoveal scotomas related to GA and scotopic sensitivity can be rationally linked to rod photoreceptor cells because of the higher density of rod cells parafoveally *(See Figure 2)* and the primary role of rod photoreceptor cells in low-light vision.[6] The disruption of rod

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photoreceptor cells is also thought to be associated with RPE cell damage due to the role of RPE cells in the regeneration of visual pigments for the vitamin A visual cycle in rods.[6] Many novel treatments currently in preclinical development or in early-stage clinical trials target pathological schemes of rod photoreceptor cell metabolism in order to slow the progression of dry AMD and protect the RPE *(See Table 1)*. The disease processes of the RPE are currently of particular interest because the Food and Drug Administration has recently begun approving treatments based on the reduction or maintenance of GA lesion size in the RPE, rather than basing drug approval on visual acuity improvements alone. Research has therefore become more focused on the development of GA rather than other pathological changes such as drusen accumulation and pigment clumping that are more difficult to measure and compare.

Figure 2. Relationship of Rod and Cone Cells

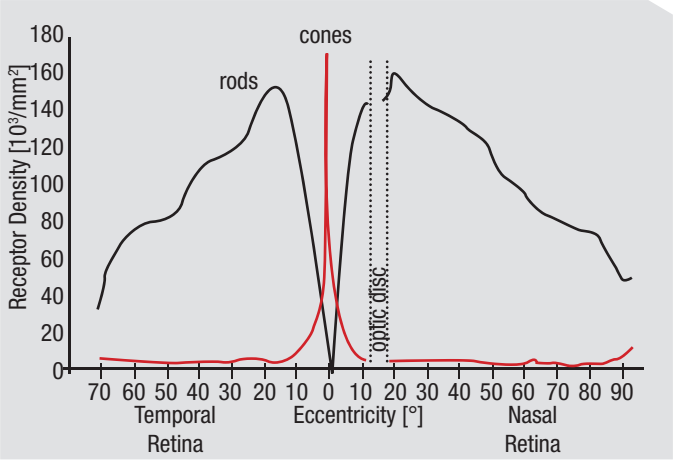

Figure 2: Relationship of rod and cone photoreceptor cells within the retina. Rod cells are preferentially located in the parafoveal region where geographic atrophy is more likely to develop, while cone cells are primarily concentrated in the fovea.

The Visual Cycle and AMD

Rod photoreceptor cells convert light energy into electrical signals through the visual cycle. In order to carry out this process, the photoreceptors of the retina are dependent on the metabolic support of the RPE for the regeneration of visual pigment and breakdown of photoreceptor byproducts.[7,8] In rod photoreceptor cells of vertebrates, 11-*cis*-retinal generated in the RPE is isomerized by light to all-*trans*-retinal, which is then reduced to all-*trans*-retinol *(See Figure 3)*. In order for the visual cycle to continue, the 11-*cis*-retinal must be regenerated in the RPE from all-*trans*-retinol with the help of the isomerase RPE65.[3] Throughout this regeneration process, the toxic metabolite retinylidene-N-retinylethanolamine (A2E) is created as a byproduct within the outer segment disks of the rod photoreceptor cells. In patients suffering from AMD, A2E and other bi-retinoid compounds are not properly digested by the RPE and disrupt RPE cell function, thus causing RPE cell death and increasing the metabolic workload of adjacent RPE cells.[9-11] This disease progression is discernible on fundus autofluorescence photography due to the distinct autofluorescent emission of A2E and related cytotoxic fluorophores *(See Figure 4)*. Areas of increased FAF as associated with A2E accumulation have been observed both at the boundaries of GA lesions and in areas of future atrophic development, indicating that areas of increased FAF precede both development and enlargement of GA lesions.[12-18]

Pathway-Based Therapies

Developing therapies for dry AMD aim to slow A2E accumulation by targeting various steps within the visual cycle in order to slow the progression of GA and protect the photoreceptors. Two oral medications are currently in clinical testing in order to determine their safety and efficacy in the treatment of GA.

The first medication, the oral agent emixustat (ACU-4429; Acucela), is a small non-retinoid molecule that functions as a modulator of isomerase RPE65, which is required for the conversion of all-*trans*-retinol to 11-*cis*-retinal in the RPE. By inhibiting RPE65, emixustat reduces the levels of 11-*cis*-retinal and suppresses rod photoreceptor function and the visual cycle, thus theoretically reducing A2E accumulation and subsequent GA development and enlargement. Emixustat is specific to the visual cycle in rod photoreceptor cells and therefore should not cause the same vitamin-A deficiency systemic effects or ophthalmic side

Table 1: Current Medications in the Pipeline for Pathway-Based Therapy for Dry AMD

Drug	Sponsor	Mechanism of Action	Clinical Study Phase
Fenretinide	ReVision Therapeutics	Retinol inhibitor	Phase II
Emixustat	Acucela	RPE65 inhibitor	Phase IIb/III
RN6 G	Pfizer	Anti-Amyloid β 40/42 antibody	Phase II
GSK933776	GlaxoSmithKline	Anti-Amyloid β 40 antibody	Phase II

Figure 3. The Visual Cycle

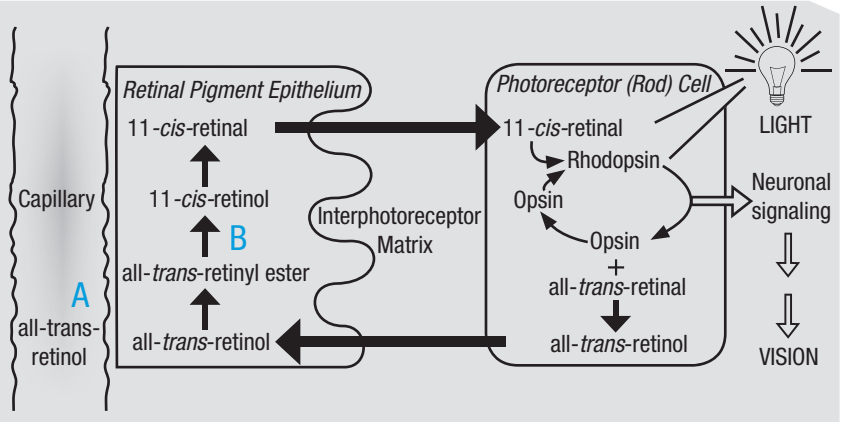

Figure 3. The visual cycle. A) Fenretinide inhibits the delivery of retinol by binding to retinol-binding protein; and B) Emixustat modulates the isomerase RPE65, which is required for the conversion of all-*trans*-retinol to 11-*cis*-retinal.

effects such as nyctalopia as do visual cycle modulators that act systemically.[19]

The Phase Ia study for emixustat has been completed (Clinicaltrials.gov identifier: NCT00942240). Forty-six healthy male and female subjects were randomized to either a placebo group or one of five doses ranging from 2 mg up to 75 mg per day. The drug was well-tolerated and exhibited a dose-dependent modulation of rod ERG signals. A Phase IIb/3 clinical trial is currently under way to determine the efficacy of emixustat in patients with GA.

The second drug therapy involving visual cycle modulation is fenretinide (RT-101, ReVision Therapeutics). Fenretinide is an oral synthetic retinol derivative originally developed to treat diseases including rheumatoid arthritis, psoriasis and various cancers. These past studies have found limited efficacy but have demonstrated long-term safety and tolerability of fenretidine.[20-25]

In the normal physiological process, the retinol necessary for the regeneration of 11-*cis*-retinal is delivered to the RPE in a complex formed by RBP, retinol and transthyretin (TTR). In circulation, fenretinide competes with retinol for RBP binding and the subsequently formed RBP-fenretinide complex is removed by the kidneys through excreted urine, thus reducing the circulating quantity of RBP.[26,27] The systemic inhibition of retinol by fenretinide is dose dependent and reversible upon drug cessation.[20-23] Because the delivery of retinol to the RPE is uniquely dependent on the binding of retinol and RBP, fenretinide treatment preferentially reduces retinol concentrations in the retina rather than other areas of the body, although visual disturbances such as delayed dark adaption have commonly been reported as a side effect of fenretinide.[20,22,23,27]

Reducing the delivery of RBP-retinol to the RPE is theorized to reduce the accumulation of A2E and related compounds and thus slow GA lesion growth. A two-year Phase II proof-of-concept trial (Identifier: NCT00429936) was designed to determine whether fenretinide-mediated reductions of RBP would lead to a reduction of lesion growth in subjects with GA secondary to dry AMD. The study utilized two doses (100 mg and 300 mg) and a placebo group. For the placebo and 100-mg groups, no correlation was observed between reductions in lesion growth and reduction in RBP levels. However, for the 300-mg group there was a clear trend for reduced lesion growth rates in patients who achieved serum RBP levels ≤2 mg/dL. Fifty-one percent of 300 mg patients who completed the two-year study achieved this level of RBP reduction. Variabilities in the production of fenretinide are hypothesized to be partially responsible for inconsistent bioavailability of administered fenretinide and fluctuations in systemic results in the 300-mg dosage group. Additionally, fenretinide treatment at both the 100-mg and 300-mg doses was associated with a 45-percent reduction of CNV incidence relative to placebo.[27] Therefore, fenretinide was found to have both dose-dependent properties for the reduction of GA lesion growth and dose-independent anti-angiogenic properties for the prevention of CNV if adequate drug bioavailability was achieved. Recently, Acucela acquired fenretinide and the combined efforts will ideally produce significant advances in visual cycle modulation and excess A2E reduction.

The theoretical mechanisms of visual cycle modulators such as fenretinide and emixustat is analogous to that of beta-adrenergic blocking agents (also known as beta-blockers) in congestive heart failure. Beta-blockers work by lowering blood pressure, thus reducing the heart rate of the patient and the force of each heartbeat. By reducing the workload of the heart, beta-blockers slow the progression of heart failure and reduce patient mortality.[28] In a similar fashion, visual cycle modulators aim to reduce the workload of the RPE by decreasing rod photoreceptor metabolism and A2E accumulation, thus potentially slowing the progression of AMD and improving patient outcomes.

Byproduct Accumulation

The chronic inflammation associated with AMD is additionally associated with a second byproduct other than A2E—amyloid beta.[29] Amyloid beta, a waste product of the central nervous system associated with diseases such as atherosclerosis and Alzheimer's disease, has been found as a differentiating compound between dry AMD eyes and control age-matched donor eyes.[30-32] Amyloid beta, which has been identified as a component of drusen, is a known activator of the complement system and may lead to damage in RPE cells and play a role in inflammation that contributes to AMD progression.[32,33] The presence of proinflammatory molecules of the complement system within drusen may stimulate chronic inflammation in the RPE-Bruch's membrane-choriocapillaris complex and induce vascular endothelial growth factor expression, thus explaining why soft drusen and theoretically amyloid beta accumulation are risk factors for CNV in AMD eyes.[32,33]

Reducing Accumulation

Amyloid diseases and drusen in AMD eyes are associated with abundant amyloid beta fibrils of various lengths. Two humanized anti-amyloid beta antibodies, RN6G (PF-4382923; Pfizer) and GSK933776 (GlaxoSmithKline), bind to amyloid beta 40/42 and amyloid beta 40 respectively in peripheral circulation in order to decrease its accumulation within the retina by sequestering the byproduct in the periphery. Animal mouse models have shown the efficacy of anti-amyloid beta antibodies in preserving photoreceptors and reducing retinal atrophy without disrupting normal photoreceptor function.[34] Both drugs have successfully completed Phase I clinical trials (Identifiers: NCT00877032

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and NCT01424436). GSK93376 is currently being tested for potential efficacy in a Phase II clinical trial (Identifier: NCT01342926) and the Phase II clinical trial for RN6G has recently resumed patient recruitment (Identifier: NCT01577381).

While the treatment of exudative AMD has transformed with anti-angiogenic therapies, therapeutic agents that prevent and delay the progression of dry AMD remain elusive. While current anti-angiogenic therapies address CNV, treatment for the underlying RPE changes and retinal atrophy is still under investigation. Ongoing clinical trials may shed light on new therapies basesd on the reduction of byproduct accumulation and the modulation of rod photoreceptor cell activity. REVIEW

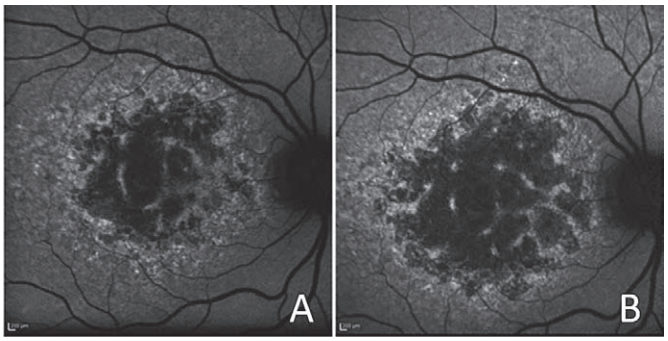

Figure 4. Progression of nonexudative AMD as visualized with fundus autofluorescence: A) Hyperfluorescence on fundus autofluorescnce concentrated at the GA lesion border in August 2009; B) Expansion of geographic atrophy among areas of past hyperfluorescence in the same patient in August 2011.

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Figure 2. Modified from Osterberg, G. Topography of the layer of rods and cones in the human retina. Acta Ophthalmol 1935:Suppl. 13:6, 1-102.

Figure 3. Modified from http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/visualcycle.html Copyright 2010.

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How to Recognize & Treat Thyroid Eye Disease

Early recognition of the clinical activity and severity of TED is crucial in determining the treatment and preserving vision.

H. Joon Kim, MD, Atlanta

Thyroid eye disease, or Graves' ophthalmopathy, is a potentially vision-threatening autoimmune disease that manifests most commonly in hyperthyroid patients (77 percent), and less frequently in euthyroid (20 percent) and hypothyroid (3 percent) patients.[1] TED can precede or succeed the thyroid disease, usually within 18 months of each other in the majority of the patients.[2] Although great variability in severity and duration of the disease can be observed, TED is ultimately a self-limiting disease that lasts about one year in non-smokers and three years in smokers.

Risk Factors

TED occurs between the 3rd and 6th decades, at a rate of 16 women and three men per 100,000.[2] Although it is more common in women, men tend to exhibit more severe disease and present at a more advanced age. Cigarette smoking is the strongest modifiable risk factor resulting in more severe disease, which is less responsive to immunosuppressive therapy. Additionally, use of radioactive iodine (RAI) for hyperthyroidism has been associated with the development or worsening of TED. However, this has become more controversial as evidence suggests that rapid stabilization of the thyroid hormones after RAI treatment can prevent adverse progression. Genetic factors appear to play a role in TED, but specific contributions have yet to be elucidated.[4,5]

Images: Ted Wojno, MD

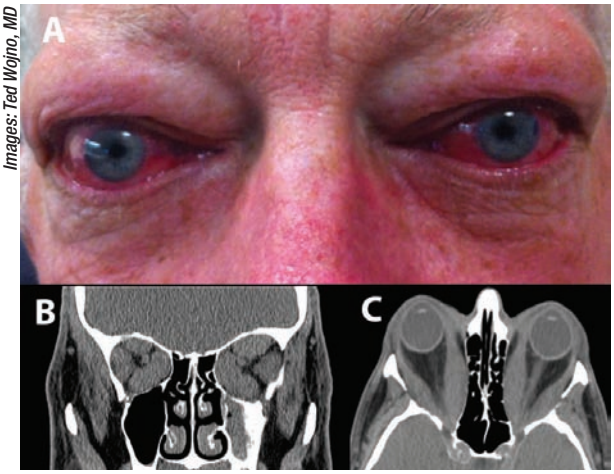

Figure 1. A) Clinical photograph of a patient with active thyroid eye disease exhibiting the following signs: bilateral proptosis with left hypertropia; bilateral upper and lower eyelid edema; erythema; retraction; and bilateral conjunctival injection. B) Non-contrast CT, coronal view demonstrating bilateral enlarged rectus muscles with apical crowding around the optic nerve. C) Non-contrast CT, axial view demonstrating fusiform enlargement of the extraocular muscles with tendon-sparing.

Pathogenesis

The pathogenesis of TED is incompletely understood, but is believed to be due to a reaction of T lymphocytes with antigens present in both the thyroid gland and the orbit. This reaction initiates a cascade of events that lead to the release of cytokines and other inflammatory mediators, resulting in proliferation of orbital fibroblasts, expansion of adipose tissue and enlargement of extraocular muscles. This inflammatory increase in the periorbital and orbital structures is responsible for the clinical manifestations of TED.[6]

Clinical Features

In general, approximately 30 to 50 percent of patients

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Table 1. Classification System for Clinical Activity Score (CAS)[9]

Pain	
	• Painful on or behind the globe
	• Pain on up, side or down gaze
Redness	
	• Redness of eyelid(s)
	• Diffuse redness involving the conjunctiva
Swelling	
	• Chemosis
	• Edema of the lid(s)
	• Proptosis increases 2 mm or more over one to three months
Impaired function	
	• Loss of visual acuity, one or more lines from the Snellen chart (with a pinhole) over one to three months
	• Decreased eye movements, any direction ≥5° over one to three months

with thyroid disease have ophthalmic manifestations, of which only 3 to 5 percent of the patients constitute the vision-threatening spectrum of the disease.[7] Patients will commonly present with complaints of diplopia, changes in the appearance of their eyes or symptoms related to corneal exposure, such as foreign body sensation, photophobia, redness and tearing. Patients will also complain of eyelid fullness or swelling and present for an evaluation for a blepharoplasty, which of course should be avoided during the active phase.

The most common and specific clinical finding for TED is eyelid retraction, occurring in about 91 percent of the patients *(See Figure 1a)*. This is followed by proptosis (62 percent); motility dysfunction (43 percent); pain (30 percent); epiphora (23 percent); and compressive optic neuropathy (6 percent).[8] Hence, in the clinical setting, it is important to measure the degree of inferior and superior scleral show, exophthalmos and motility. Oftentimes, patients will complain of soreness or a "pulling" sensation during the motility exam, especially in upgaze. The degree of lagophthalmos should be noted, and is often helpful to correlate with conjunctival and corneal changes. Chemosis is an extremely common finding, while corneal changes could range from mild punctate epithelial erosions to ulcerations and stromal thinning, usually along the inferior half. Additionally, close attention must be paid to the pupil exam to assess for compressive optic neuropathy. Clinical signs are usually bilateral but can often be asymmetric or, less frequently, unilateral. Systemic signs can also aid in determining the status of their thyroid disease or even lead to the diagnosis of thyroid disease. These signs are often nonspecific and include fatigue, weakness, cold or heat intolerance, anorexia, skin or hair changes, changes in their sleep or appetite and mood instability.

These signs will often allow for a clinical diagnosis of TED, and also determine the phase of the disease. TED emerges in the active phase, where periorbital and orbital inflammation will lead to the manifestation of the ocular symptoms. This phase usually lasts about one to two years before it spontaneously remits. The active phase is then followed by a plateau phase, where symptoms generally stabilize or may show some improvement before entering the inactive phase. Maarten P. Mourits, MD, PhD, and colleagues described a Clinical Activity Score to aid in determining the phase of the disease *(See Table 1)*.[9] One point is assigned to each of the 10 listed symptoms or signs and a score of 3 or more indicates active disease. The phase of the disease will then ultimately determine the indicated workup and treatment.

Differential Diagnosis

Depending on the presenting symptoms, further workup can be necessary to rule out other possible diagnoses. For those patients presenting with signs of orbital inflammation or congestion, orbital cellulitis, idiopathic orbital inflammation (IOI), and other inflammatory conditions, such as sarcoidosis, should be considered. However, infectious causes are often linked to a history of a recent illness, especially sinusitis, or related systemic findings, such as a fever. Patients with IOI usually report a more acute onset, with pain being the most prominent symptom. A CT or an MRI can show an orbital abscess and/or sinus disease to clinch the diagnosis of an orbital cellulitis, while a tendon-involving enlargement of the extraocular muscles makes IOI a more likely etiology *(See Figure 2)*. Sarcoidosis frequently reveals an enlarged lacrimal gland that necessitates a biopsy.

For unilateral cases, orbital tumors or traumatic causes such as carotid-cavernous fistula should be suspected given the right history. Although nonspecific, tumors can often show globe displacement, while a C-C fistula will exhibit classic signs, such as "corkscrew" vessels, a discernible bruit and pulsatile exophthalmos. Again, diagnostic imaging can confirm the diagnosis *(See Figure 2)*. With primary signs of motility dysfunction, cranial nerve palsies, chronic progressive external ophthalmoplegia (CPEO), or myasthenia gravis should be ruled out as well. However, with these diagnoses, patients lack other classic TED findings, such as eyelid retraction, proptosis and orbital congestion. Additionally, CPEO and myasthenia gravis will frequently present with

ptosis. It is important to keep in mind, though, that myasthenia gravis is significantly more likely in patients with thyroid disease.

Workup

A thorough history and a clinical exam are often adequate to make a diagnosis of TED, and ancillary testing will assist in determining the clinical activity and severity of the disease. Visual field testing should be performed in patients with active TED, especially with concerns of compressive optic neuropathy. Findings are nonspecific, but can reveal enlarged blind spots, generalized constriction or paracentral or arcuate defects. CT or MRI will often show tendon-sparing fusiform enlargement of the extraocular muscles, with the inferior and medial rectus muscles being the most commonly involved *(See Figure 1, B & C)*. Imaging will also evaluate for apical crowding to assess for compressive optic neuropathy. For those patients where the ocular symptoms precede the diagnosis of thyroid disease, it is important to obtain a thyroid panel. For atypical cases, a biopsy could be indicated.

Management

Once initiated, the eye disease functions and progresses independently of the thyroid disease, and thus should be managed independently. Stabilization of the thyroid levels should be achieved together with an endocrinologist. In the event that radioactive iodine is utilized to correct the thyroid disease, concurrent use of oral steroids tapered over a three-month period can prevent or minimize the effects on the eye disease.[10] Modification of risk factors, especially smoking cessation should be strongly encouraged. Due to the self-limiting nature of the disease, observation or conservative therapy with lubrication is often sufficient for patients with minimal disease.

For patients in the active phase, the

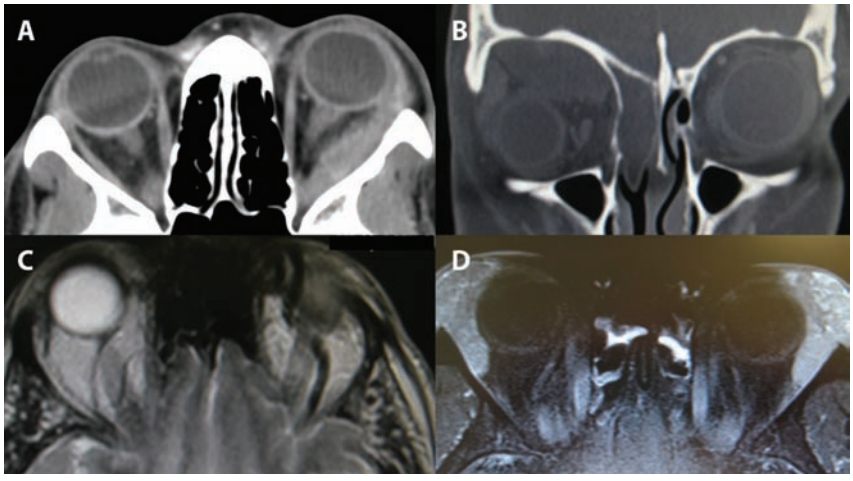

Figure 2. A) Contrast CT, axial view demonstrating tendon-involving enlargement of left lateral rectus muscle, more consistent with idiopathic orbital inflammation. B) Noncontrast CT, coronal view demonstrating a large abscess along the roof of the right orbit. Associated sinus disease is also shown. C) MRI with gadolinium, axial view demonstrating significantly enlarged left superior ophthalmic vein suggestive of a C-C fistula. D) MRI with gadolinium, axial view demonstrating bilateral enlargement of the lacrimal glands. Biopsy was consistent with sarcoidosis.

emphasis of treatment is decreasing or inactivating the inflammatory process and preserving vision. This is typically achieved with immunomodulation, radiotherapy and/or surgery. Oral corticosteroids (0.5 to 1mg/kg) tapered over a three to six month period, or in more severe cases, weekly IV steroids, have been utilized. Steroids prove especially useful in reducing pain, soft tissue improvement (i.e., eyelid edema and erythema), and temporizing optic nerve compression. Despite the benefits, the side-effect profile of corticosteroids prevents their long-term use. More side effects were noted with oral steroids including weight gain; hyperglycemia; hypertension; anxiety; mood lability; skin changes; gastrointestinal manifestations; and insomnia. For those who cannot tolerate the systemic effects of steroids, periorbital injections of steroids have been employed, but with less significant impact. Nonsteroidal immunomodulators, such as cyclosporine and rituximab, have emerged as alternatives. Thus far, their high cost, wavering efficacy and questionable side-effect profile have prevented them from being a first-line treatment.[7,10,11,12]

Although controversial, external beam radiation therapy, usually at very low doses (20 Gy), can be effective in achieving local control of active TED. Studies have shown radiotherapy to be the most useful in improving motility dysfunction. Development of cataract, radiation-induced retinopathy, optic neuropathy and secondary tumors are all concerns related to radiotherapy, but the risk remains low at the doses utilized for TED. Underlying diabetic retinopathy can potentiate the effects of radiation retinopathy, and thus is usually contraindicated for radiation. Greater benefit has been noted when steroids are used concurrently with radiotherapy.[11,12]

It is generally recommended that surgical intervention be postponed until the patient has entered the inactive phase or stabilization of his symptoms for at least three to six months. One exception is when the vision is threatened from compressive optic neuropathy or severe proptosis with resultant corneal ulceration or stretch optic neuropathy. In this instance, orbital decompression surgery is often employed as the first-line therapy to preserve vision. In general, removal of one or two orbital walls and/or orbital fat is performed to decompress the optic nerve and allow the globe to retract. Once stability is achieved, strabismus surgery, if necessary, can then be performed, followed by eyelid surgery to correct the retraction as needed. Cosmetic surgery, such as a blepharoplasty, should be performed last and with caution.[11]

TED is a relatively uncommon orbital condition that requires a multidisciplinary approach to its diagnosis and management. Early recognition of the clinical activity and severity is crucial in determining the appropriate treatment that could ultimately result in preservation of vision. REVIEW

Dr. Kim is an assistant professor of ophthalmology at the Emory Eye Center in Atlanta.

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In-Clinic IOP: How Much Does It Tell Us?

Determining the clinical value of mean vs. peak IOP—and the possible importance of IOP fluctuation—remains a challenge.

Arthur J. Sit, SM, MD, Rochester, Minn.

Reduction of intraocular pressure is currently the only known treatment for glaucoma. How aggressively we work to lower IOP is determined, at least in part, by the risk of further progression of disease. However, IOP is variable, and more than one IOP parameter could potentially be assessed and modified—at least in theory. Here, I'd like to discuss the pros and cons of different IOP-related parameters, in terms of their potential usefulness in the clinic.

Mean IOP vs. Peak IOP

The IOP parameter that has been most extensively characterized is mean IOP, which has been the primary parameter assessed in most of the large clinical trials looking at risk factors for progression, including the Collaborative Normal-Tension Glaucoma Study, the Advanced Glaucoma Intervention Study, the Early Manifest Glaucoma Trial and the Ocular Hypertension Treatment Study. The data from those studies confirmed that mean IOP is a very important predictor of both the risk of glaucoma progression and the risk of developing glaucoma in patients who have ocular hypertension.

Ironically, although most of our clinical trial data tells us about the significance of mean IOP, most of us are probably basing our clinical decisions more on peak IOP than mean IOP. In a typical busy practice, we'll create a pressure target—a peak IOP that we want the patient to remain below—and then we'll check the patient's pressure periodically as he or she comes in for routine visits. If the measured IOP is above the target IOP, that's when we tend to react and alter our therapy. We may recheck the IOP to ensure that the measurement was not anomalous, but we are still reacting to a peak IOP and not the mean.

Unfortunately, we have much less objective information about the clinical significance of peak IOP than we do about mean IOP. Peak IOP is not what the clinical trials were originally designed to look at (although peak IOP has been looked at retrospectively). This doesn't mean that mean IOP is more important than peak IOP; we simply have more data regarding mean IOP.

In any case, the practical reality is that when you can only take one measurement every few months, thinking in terms of peak IOP rather than mean IOP makes more sense; it allows us to proceed despite the limitations of the data we have available to us. That's why a typical clinical practice operates that way, and that tendency is unlikely to change until we have tools that give us better data.

The Fluctuation Factor

Fluctuation of IOP as an independent risk factor for glaucoma is an area that has been of significant interest recently. Many patients with seemingly good IOP control (as measured in the clinic) continue to get worse, and IOP fluctuation is a plausible contributor to this. Although the large clinical trials have provided extensive useful data regarding mean IOP, they were not designed to reveal whether any other IOP parameters might be useful as well. Nevertheless, retrospective data analysis to determine the significance of IOP fluctu-

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ations has been performed on the data from most of the major clinical trials in glaucoma.

Unfortunately, research into the significance of IOP fluctuation hasn't produced a lot of conclusive information so far, for two reasons. First, there are many levels of fluctuation and multiple ways to analyze them. Second, the technology to monitor fluctuation is still in its infancy, so the data we have to base predictions on, and our ability to collect data, are very limited.

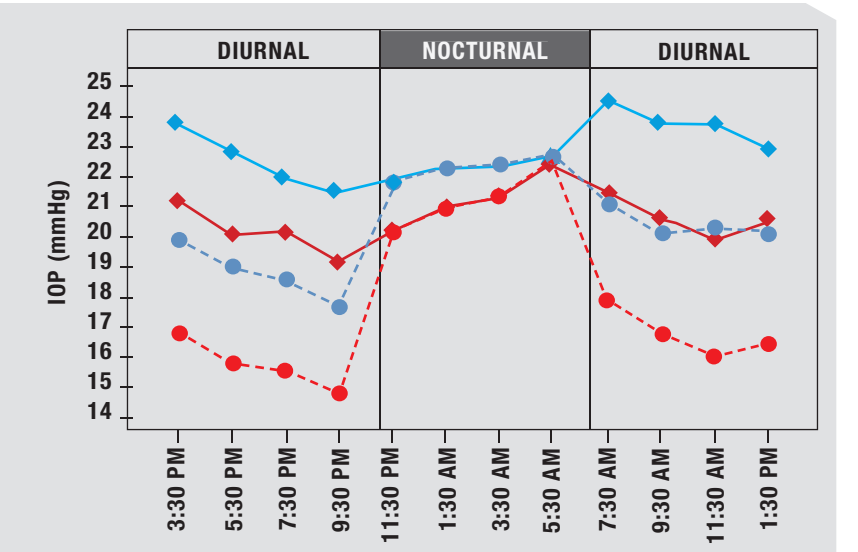
One issue is the scale of time over which we look at fluctuations. We know from animal studies that fluctuations may be occurring almost constantly on a second-to-second and minute-to-minute basis. Larger-scale fluctuations also occur over the course of a 24-hour period, as has been documented in animals as well as 24-hour human sleep-lab studies. In addition, there are even longer fluctuations that occur over weeks to months, and others that occur over years. The relative importance of these different levels of fluctuation is not yet clear.

At the minute-to-minute level, data collected using implantable transducers in rabbits and monkeys demonstrate that pressures fluctuate very significantly over very brief periods of time, and do so almost constantly.[1,2] The clinical significance of these short-term fluctuations, however, is unknown. Continuous 24-hour IOP monitoring is one of the holy grails of glaucoma research, and there have been notable technological advances over the past few years. Nevertheless, devices for routine clinical use that can deliver the type of IOP data we can currently gather from animals are not yet available. Until we can measure these fluctuations in humans, their significance in the development and progression of glaucoma will likely remain unclear.

We do have some limited data regarding the impact of diurnal (daytime) fluctuations. One study done by Sanjay Asrani, MD, for example, looked at diurnal fluctuations in IOP measured using home tonometry and found that glaucoma patients who had larger fluctuations over the course of a day were more likely to progress.[3] But home tonometry is not available to most patients, and those study results should be repeated using other measurement methods.

In terms of circadian variability, it's well-established based on the sleep laboratory research of Robert Weinreb, MD, and John Liu, PhD, and colleagues, at the Shiley Eye Center, University of California San Diego, that there's a rise in intraocular pressure when patients lie down to sleep. *(For example, see figure above.)* However, the magnitude of that rise is greater in normal patients than in glaucoma patients, so the difference between diurnal and nocturnal IOP is unlikely to be an independent risk factor for glaucoma. However, systemic blood pressure is lower at night in most people, and this could combine with a higher IOP at night to compromise blood flow to the optic nerve. For now, whether or not the nocturnal IOP rise is an independent risk factor for glaucoma remains to be demonstrated.

24-Hour IOP: Early Glaucoma vs. Normals; Sitting vs. Supine



Twenty-four hour IOP patterns in 24 patients with newly diagnosed, untreated early glaucomatous changes (blue lines) and 24 healthy controls (red lines). Measurements were taken with patients sitting (circles) and supine (diamonds). (Based on Liu, *et al*, 2003.[9])

The Large-scale Trials

Most of the published research concerning IOP fluctuation as a risk factor for glaucoma has examined long-term fluctuations over months and years, using the data from the large clinical trials. However, what those studies have found is somewhat contradictory. Several papers have been published based on data from the AGIS study, for example. The first paper found that patients with larger standard deviations in IOP between visits were more likely to progress, using visual field scores as a measure of severity. However, a subsequent analysis took into account the fact that patients who have glaucoma progression probably have a change in their therapy in order to lower

their pressure, a change that would automatically create long-term IOP variability. Once they took that into account, it was only patients who had low mean IOPs who seemed to have IOP fluctuation as a risk factor for further progression.

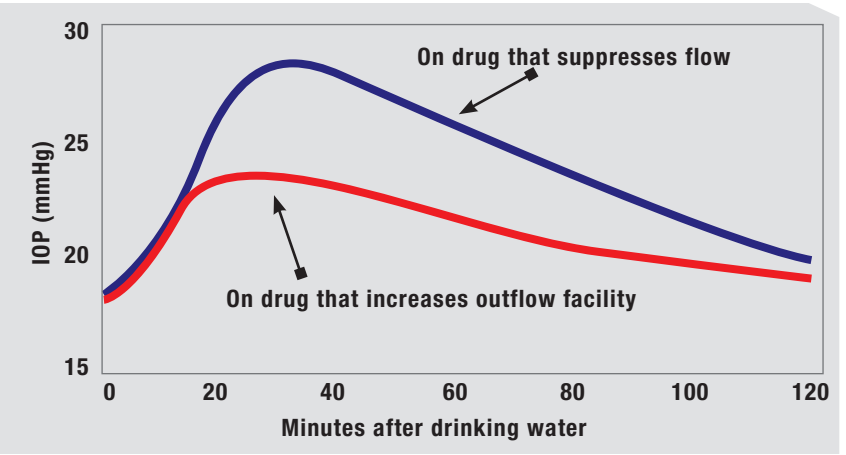
The reason for that is not really clear. One explanation might be that we're thinking about IOP variability in the wrong way. Most studies look at IOP variability in terms of things like range and standard deviation. But if you think about IOP variability in terms of a percentage change instead of an absolute change, then at a high pressure, say a pressure of 30 mmHg, a 2-mmHg fluctuation is a pretty small percentage change up or down. On the other hand, if you're at 10 mmHg and you have that same 2 mmHg variability, that's a large percentage change. That 2-mmHg fluctuation may actually have a greater effect in terms of movement of the lamina cribrosa and deformation of the optic nerve head at 10 mmHg than at 30 mmHg.

Other studies have also looked at the impact of long-term inter-visit IOP fluctuation. The CIGTS study compared medical treatment for glaucoma vs. surgical treatment; IOP fluctuation data from that study indicated that IOP fluctuations were a risk factor for progression in medically treated patients but not in surgically treated patients. That appeared to be true even though the magnitude of the fluctuation the patients experienced was pretty much the same in the two groups. Again, an explanation for these findings is not clear.

Another related, as yet unpublished finding was presented at the American Glaucoma Society Annual Meeting last spring by Mae O. Gordon, PhD, based on data from the OHTS trial. That data indicates that IOP variability in the observation group—those not being treated—did not correlate with an increased risk of converting to glaucoma. But in patients who were being treated medically, IOP variability did increase the risk of converting from ocular hypertension to glaucoma.

The idea that medical treatment may somehow potentiate the effect of IOP fluctuations on progression is interesting, but again, we don't have a good explanation for these findings at this time.

IOP Fluctuation in Eyes Treated With Different Types of Drugs



A computer simulation of IOP change after drinking one liter of water in patients using an aqueous suppressant vs. a drug that enhances aqueous outflow. Prescribing the latter type of treatment might result in a better quality of IOP control—and less fluctuation—over the course of the day. (Based on Brubaker, 2003.[10])

Maximizing Measurements

With better technology in the future, we should be able to gather much more IOP-related information. In the meantime, there are a few things we can do to take advantage of what we currently know about mean and peak IOP and the possible impact of IOP fluctuation.

First of all, we can try to maximize the value of the in-office measurements we take today with a few simple strategies:

• ***Take IOP measurements of each patient at different times of day.*** Research has clearly shown that a single IOP measurement is not a good indicator of the patient's IOP pattern over a 24-hour period. Work done by Tony Realini, MD, for example, looked at the repeatability of pressure measurements taken at a specific time of day on different days, and how well they reflect diurnal patterns.[4,5] That data showed that one measurement is really not predictive of subsequent IOP measurements taken at the same time of day. So, doing multiple measurements at different times of day would be helpful.

• ***Take IOP measurements more often.*** This would allow us to get a better sense of the patient's mean IOP. Of course, taking more measurements would also involve getting the patient into the office more frequently, which would be difficult when we're all seeing more and more patients in a shorter period of time. (It would also be more of a burden for the patient.) And, it might raise questions regarding reimbursement. So practical considerations make this a challenge to implement.

One change that might help would be the development of a means for patients to accurately measure their IOP at home. Some instruments that don't require an anesthetic have been

tried for home use (such as the air-puff tonometer and rebound tonometer); however, using them at home involves significant cost for the patient and may not be suitable for patients with limited dexterity. And even though this type of arrangement would be better than having one measurement every three or six months, it still might not give us the information we really want. What we really need is a good profile of what the IOP is doing over the course of a 24-hour day, and over multiple days.

Minimizing Fluctuation

To date, we don't have conclusive proof that fluctuating IOP impacts a patient's risk of progressing, but I believe there's enough suggestive evidence that fluctuation may be a risk factor for glaucoma—at least in some populations—that it's worth tailoring therapy to minimize fluctuation, as long as there's minimal risk to the patient. Here are a few things we can do to accomplish this:

• ***Consider tailoring medications to minimize fluctuation.*** For example, certain medications provide smoother IOP control; any medications that suppress aqueous production will cause larger IOP fluctuations throughout the day, just because they reduce fluid flow but don't change the flow resistance. In that situation anything that would normally perturb your IOP anyway, such as drinking a bottle of water, will cause your pressure to go up, and the rise will be larger than if you were on a different medication that improved outflow facility. *(See diagram, facing page.)* For that reason, using a medication such as a prostaglandin analog, which enhances aqueous humor outflow, might provide a better quality of IOP control—and less fluctuation—throughout the day.

You can also choose to avoid medications that don't work at night. Drs. Weinreb and Liu and colleagues at the Shiley Eye Center have produced a large body of work from their sleep laboratory demonstrating that not all medications are effective at night. They have demonstrated that beta blockers and alpha agonists have minimal efficacy at night, while prostaglandin analogs and carbonic anhydrase inhibitors continue to have good nocturnal efficacy, although less than during the daytime. If the choice of medication doesn't result in increased risk or prohibitive cost for the patient, selecting prostaglandin analogs or carbonic anhydrase inhibitors may benefit the patient by

helping to limit 24-hour IOP fluctuation.

• ***Consider performing laser trabeculoplasty.*** One of the less-often discussed results of using a procedure such as selective laser trabeculoplasty is that IOP fluctuation is reduced.[6,7] The likely explanation is that it enhances outflow facility, leading to a more consistent IOP over the course of the day. In addition, it's a very low-risk procedure. Given that it smoothes out IOP fluctuation, it makes sense to try it in patients whose IOP seems well-controlled but who continue to get worse.

In the United States, clinicians still don't perform SLT very frequently, often because of the perception that it doesn't reduce IOP as much as other alternatives. I believe that perception is partly the result of the frequent use of SLT as a last resort. Once a patient is already on maximum medical therapy, even adding another drop will have minimal effect, so it shouldn't be a surprise that SLT doesn't cause a major change under these conditions.

In my experience, you'll see a larger effect if you perform SLT earlier in the course of treatment, before the patient is on multiple medications. I think it's a reasonable option to offer earlier in the treatment spectrum, not only to reduce IOP, but also to achieve a better quality of IOP control—i.e., reduced fluctuation—than you might get with something like a beta-blocker.

• ***Consider the impact of body position.*** In clinical situations we virtually always measure pressure with the patient sitting in a chair at a slit lamp, but it's long been known that pressure varies with body position. Certainly IOP increases when we lie down. In fact, some studies have found that measuring pressure when the patient is supine is somewhat predictive of IOP at night. *(See diagram, p. 105.)*

Our group did a study in which we measured IOP in different body positions: sitting upright or sitting with neck flexed or extended, lying on your back, or lying on your side.[8] It turned out that just about any body position results in a pressure that is higher than when you're sitting upright at a slit lamp.

One useful ramification of this is that we can advise our patients to be aware of this factor. Certainly we all need to lie down and sleep, but individuals with glaucoma can try to avoid sleeping face down; sleeping face down can produce much higher intraocular pressures, not just from the body position, but also because of compression against the eye. I also advise patients who do yoga not to do head-stand positions, and patients who have highly asymmetric disease and sleep on their side may benefit from sleeping on their back or on the side that puts the worse eye above the better eye. Sleeping in a head-up position can also reduce the nocturnal IOP peak. However, the clinical benefit of adopting or avoiding specific head and body positions is currently unknown.

No Guarantees

Unfortunately, we don't have any conclusive evidence that reducing fluctuation will prevent or minimize progression, and doing a controlled, randomized study to demonstrate this would be difficult. We know from existing studies that we have to manage mean IOP; it's unethical not to. So anyone with glaucoma in the study would have to be treated to lower the mean IOP. If both groups are lowered to the same level, any remaining difference caused by fluctuation might be tiny in comparison and difficult to demonstrate, especially given today's imprecise means of measuring fluctuation. That means the study would have to be very large to reveal a significant difference—assuming a difference appeared.

In the meantime, we can't even be certain what the variability we encounter in the clinic really means. Most of the IOP fluctuation that we're measuring may just be because of the time of day, or because someone had a cup of water right before they came in for their exam. So sorting out what is really reflective of IOP variability over a 24-hour period is going to be difficult. This will hopefully change as new technology for continuous monitoring of IOP emerges, but for now we have to operate on the assumption that fluctuation may be important to a patient's prognosis, and do what we can to minimize it when the risk to the patient is acceptable. REVIEW

Dr. Sit is an associate professor of ophthalmology at the Mayo Clinic in Rochester, Minnesota.

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Dry-Eye Tests: Reading Is Fundamental

A look at the damage dry eye causes and how reading tests might be good gauges of the disease's clinical effects.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and Lisa M. Smith, Andover, Mass.

Ophthalmologists can agree on one point: The bottom line for patients is how their visual symptoms affect their daily tasks. While eyesight can be devastated by diseases such as cataract and macular degeneration, the ocular surface changes brought on by dry eye can also be an obstacle to a patient's visual functioning and can severely affect what we now know is one critical aspect of disease management: quality of life. Dry eye-induced changes in visual function are more subtle and transient compared to permanent vision loss, yet tasks such as driving, watching television and especially reading can be profoundly affected,[1] and these detrimental effects on visual function are now widely accepted.[1-4] Among daily tasks, reading remains one of the most important.

In this article, we'll take a look at how we assess reading performance, how objective reading tests differ and which tests may be more applicable to measuring subtle changes incurred by ocular surface damage.

Dry Eye's Effects

Three phenomena account for visual disturbances in dry eye: tear-film breakup; increased blink rate; and corneal desiccation. The tear film is necessarily transparent, a complex and dynamic cocktail of lipids, water, solutes and mucins that is constantly refreshed with every blink, spreading over the exposed anterior surface of the eye and ensuring clarity, comfort and defense against infection. Dysfunction of any single component will destabilize the tear film, causing it to thin and eventually break up on the corneal surface, leading to evaporation and visual distortion.[5] This degradation occurs even in normal individuals in states of prolonged staring or in tasks of heightened concentration that necessitate suppressing blink rate,[6] and we all know shortened time to tear-film breakup is a routine diagnostic indicator for dry eye. The drying cornea sends out signals stimulating blinking, in a defensive effort to refresh tears. When tear-film instability occurs repeatedly, the cornea is compromised and cells begin to die, becoming observable with fluorescein staining. These areas of damage, particularly in the central cornea,[7] can chronically disturb visual function already hindered by an increased blink rate.[8]

How do we measure these subtle changes in visual function in dry eye? How can we determine that a tear substitute or disease-modifying therapeutic is improving visual function? One endpoint is blurred vision, a symptom patients are routinely surveyed about in clinical trials as part of an overall visual assessment. The other widely implemented instrument is the QoL questionnaire, which includes questions addressing visual function as well as other symptom assessments. Examples of questionnaires include the Ocular Surface Disease Index,[7] the National Eye Institute Visual Functioning Questionnaire,[8] the Standard Patient Evaluation of Eye Dryness,[9] the Impact of Dry Eye on Everyday Life[10] and the Dry Eye Questionnaire.[11] All are used quite frequently in clinical trials. We have developed a simple five-part questionnaire, the Dry Eye Quality of Life Questionnaire, in which one domain specifically queries the disturbance in visual tasking graded by frequency and severity of occurrence. *(Pollard S, et al. IOVS 2004;45:ARVO*

This article has no commercial sponsorship.

E-Abstract 82) The daily activity most influenced by dry eye was found to be reading, as reported by 73.5 percent of dry-eye patients. Despite their value, a drawback of all these questionnaires is that they rely on subjective memory, much like patient diaries.

Reading as a Clinical Endpoint

Recent work has taken visual function assessment one step further by comparing reading tasks in dry-eye and normal subjects. Previous studies at Ora have examined blink alterations in dry eye and visual acuity decay at distance vision using the interblink interval visual acuity decay test.[12] Other studies assessed menu and normal reading rates as possible links to visual function, particularly in subjects with central corneal staining.[13] One recently published study by Fullerton, Calif., researcher William H. Ridder, OD, PhD, confirmed our previous finding that reading rates were lower in dry-eye versus normal subjects.[14] Tokyo's Katzuo Tsubota, MD, and coworkers have also recently published studies demonstrating that their visual acuity decay metric is modifiable with treatment.[15,16]

Reading tests can be broken down into three main categories: 1) those that are used in education to gauge linguistic development, in which reading comprehension and reading age are important metrics; 2) those that assess reading acuity, or critical print size at which a subject can accurately read text, and which might be more applicable to low-vision contexts; and 3) reading speed, which appears to be the endpoint that might most accurately reflect subtle changes in visual function.

Reading acuity tests include the Sloan M cards,[17] the Pepper Visual Skills for Reading Test,[18] the Minnesota Low Vision Reading Test (MNREAD)[19] and the Radner Reading Charts.[20] The Sloan M cards were designed to measure reading at the subject's acuity print size, and are not intended for use with magnification, and are, therefore, of limited use in low-vision assessments. The Pepper Visual Skills for Reading Test evaluates reading in the subject's preferred lighting, magnification and viewing distance (character size) to provide a more accurate assessment of how low vision interferes with everyday reading *in situ*.

> come see the play look up is cat not my dog for you to the cat up dog and is play come you see for not to look my you for the and not see my play come is look dog cat to up dog to you and play cat up is my not come for the look see play come see cat not look dog is my up the for to and you

The Wilkins Reading Test uses simple words repeated in a random order that creates visual stress. Reading rates for this and other tests may be applicable as measures of visual function in patients suffering from dry-eye disease.

The MNREAD is the most cited of the acuity tests, and consists of single simple sentences with equal numbers of characters. The sentences use a syntactical structure and vocabulary at the second to fifth grade level to minimize cognitive and lexical demands, and are repeated in decreasing order of size. By plotting reading speed against print size, a function is created with a large plateau of peak reading speed and a decline for text presented at smaller or very large print sizes. The MNREAD is computer-based, although a printed card version is also available.[20] This test is aimed at low-vision readers and might not be sensitive enough for assessments of normal-range, dry-eye readers.

The Radner Reading Charts were developed on the basis of the concept of reading optotypes for the standardized measurement of both reading acuity and speed. Print sizes are logarithmically scaled (logRAD) to permit statistical analysis, and results obtained can be compared to other logarithmically scaled vision systems (e.g., logMAR). To guarantee accurate, reproducible and standardized measurements of reading acuity and speed at every viewing distance, these sentence optotypes were created to minimize variation and to keep the geometric proportions as constant as possible at all distances. A series of test sentences was developed. The sentences are highly comparable in terms of the number of words (14 words), word length, number of syllables, position of words, lexical difficulty and syntactical complexity. The Radner test has an advantage over other reading acuity tests in that it can also be used to define reading speed.[20]

Standardized paragraph texts, known as IReST, have been developed in multiple languages by Susanne Trauzettel-Klosinski, MD, and co-workers at the University of Tubingen in Germany.[22] This test might be a more appropriate standardized means of assessing reading speed than sentence-based tests. The argument is that continuous text is a better predictor of real-world reading performance, though sentences must be standardized and homogenous in syntax and character length. Texts have been developed by linguistic experts to obtain low within-subject variability among passages. The authors suggest their use as an endpoint before and after interventions. Standardization across languages is an added advantage that allows this tool to be used in

international clinical trials.

The Wilkins Rate of Reading Test consists of a paragraph of simple words without context or punctuation, read out loud, with time and errors counted.[23] It was originally developed for the testing of disabled readers or children, and to gauge the effect that colored overlays have on reading. Many visual difficulties with reading seem to emerge when text is presented in a long paragraph with closely spaced lines and letters. The theory of visual stress, proposed by Arnold Wilkins, PhD, at the University of Essex in England, is based on the fact that certain patterns or stripes can induce seizures, migraine and perceptual distortions in susceptible subjects. The test is designed to compare an individual's performance under one set of conditions with that of another, and thus might be suitable for evaluation before and after an adverse environmental challenge or therapeutic manipulation.

At Ora, we implement a Controlled Adverse Environment to exacerbate a patient's signs and symptoms of dry eye under highly controlled conditions, testing how these and associated endpoints like reading are affected by treatment. The Wilkins test is unique in that it is not designed to compare one individual subject with others of the same age or ability. In fact, reading tests are generally most useful when performed before and after treatment, and not across parallel groups, unlike the conventional, statistical comparative method used in most clinical trials in dry eye. A change from baseline reading rate as a primary endpoint would eliminate the considerable internal variables inherent in reading rate.

We have studied dry-eye and normal subjects using the MNREAD, Radner, Wilkins and IReST tests, modifying them to our specific needs. Changes include assessing blink rates during testing, measuring signs and symptoms of dry eye before and after tests, or the addition of forced-stare and altered contrast sensitivity reading tests. One problem when entering the realm of visual function tests is the potential confounding variability that lies in the psychomotor and neurocognitive functioning of subjects.[24] Factors such as age, education, depression, mild neurocognitive loss[24] and fatigue and/or sleepiness in particular[25] must therefore be carefully monitored, as they can affect the outcome of these visual function tests, particularly in the aging dry-eye population. To assure a stable baseline and minimize these known confounding variables, we combine these reading tests with tests of sleepiness, fatigue, depression and basic neurocognitive function. Results have been promising, demonstrating not only the ability to distinguish between dry-eye and normal subjects but also to detect improvements in testing after tear substitute use.

With Food and Drug Administration recognition of the dissociation of symptom alleviation from significant sign improvement in dry eye,[26] and the extreme difficulty in proving that a dry-eye therapeutic is effective for either of these conventional endpoints, reading might prove to be a clinically relevant future endpoint in dry-eye clinical trials. The unique combination of quality of life, patient-reported outcomes and signs such as tear-film breakup and keratitis that coalesce in a global assessment such as reading could provide us with a concrete way to gauge improvement in a patient's life; and that, ultimately, is what patients are searching for when they step into our offices. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Ms. Smith is a medical writer at Ora Inc.

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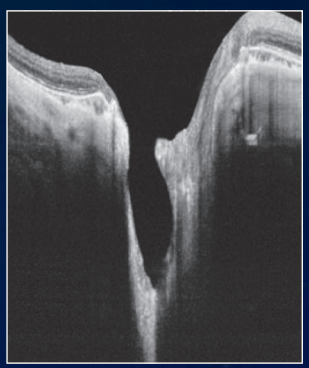
Clinical Advantages of Swept Source OCT and New Non-Damaging Laser Treatments



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Robert Weinreb, MD	University of California San Diego	*"New Swept Source OCT for Glaucoma: Improvements and Advantages"*
Richard Spaide, MD	Vitreous, Retina, Macula Consultants of New York	*"OCT Imaging of the Choroid and Beyond"*
Paulo Stanga, MD	Manchester Royal Eye Hospital	*"Clinical Efficacy of Non-Damaging Treatment Options with PASCAL Laser"*

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Tackling the Tough Refractive Cases

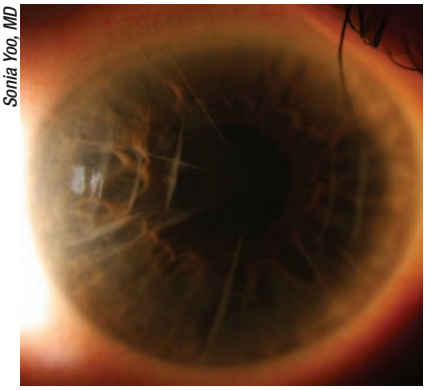
These patients will put your refractive surgery skills to the test. Here's expert advice on how to handle them.

Walter Bethke, Managing Editor

Physicians say that any refractive surgeon worth his salt can perform laser vision correction on the healthy low myope with a thick, normal cornea. It's the borderline cases—those with a history of radial keratotomy or a past suggestive of herpes simplex, for instance—that really test the surgeon's mettle. Here, expert refractive surgeons share their thought processes and surgical approaches to three kinds of tough refractive surgery cases.

Herpes Simplex

"A simple, straightforward answer is that when you read the PI booklets for the various excimer lasers, herpes is listed as a contraindication," says Sonia Yoo, MD, a cornea specialist and refractive surgeon at the University of Miami's Bascom Palmer Eye Institute. "There are cases, though, of patients who have had a history of keratitis or a remote history of uveitis in whom there's not a definitive diagnosis of herpes. It's presumed to be herpes, but there is no viral culture that proved it. So this type of patient may come in with no recurrences of those events and who is on no prophylactic medication, and who really wants refractive surgery. These cases may be candidates for LVC with proper counseling, perhaps even with a perioperative course of oral antivirals to help reduce the risk. Essentially, the risk we're concerned about is that the excimer, which is UV light, will cause dormant herpes to reactivate, since we know that UV light can cause reactivation." In this type of patient where it's not clearly herpes, Dr. Yoo says she'd start an antiviral a week or two prior to the refractive surgery and continue it for several weeks afterward.



Sonia Yoo, MD

Getting a reliable refraction is important when faced with a previous-RK patient.

Stephen Pascucci, MD, of Bonita Springs, Fla., says that in a patient with herpes, he'd also avoid any topical antiviral agents. "These agents can be, in their own right, toxic to the corneal surface," he says. "Systemic medications are the way to go.

"Obviously, a good informed consent is important," Dr. Pascucci adds. "This is so the patient understands that a recurrence during the immediate postop period is a real possibility, but not overly common."

Dr. Pascucci thinks LASIK might be preferable to PRK in these patients. "I don't think they have the healthiest epithelium, there's a relative degree of anesthesia and they probably have a little more dry eye on that side—just probably," he says. "I wouldn't want to stress the corneal epithelium and wind up with a non-healing defect, which would certainly complicate the healing and the outcome of the surface ablation. So my vote would be for a LASIK flap in these patients."

Previous RK

Surgeons say that there are many factors at play in the post-RK patient.

This article has no commercial sponsorship.

"Typically, these patients are hyperopic with some astigmatism," says Vancouver, Wash., surgeon Brian Will, who has done many of these cases. "As such, they're quite debilitated, since they have no good near or distance vision. They're very frustrated. They have a multifocal cornea as well, and many times their optical zones are pretty small. A surgeon in my area did a lot of RK, including 64-cut RKs with cross-T cuts—pretty much everything you should never do. However, I've operated on a few of those and they have done extremely well."

Dr. Will says the flap creation is key. "There are several things to consider," he says. "The incisions will tend to separate a bit. Years ago I did some of these cases with the microkeratome and when the pressure went up to 150 mmHg with the suction applied there were times I almost worried that the eye would come apart. But using the femtosecond suction application, the pressure goes up to maybe 70 mmHg, so you can turn on the vacuum and not be concerned that you're going to have a wound dehiscence. That said, the flap itself is more prone to wound dehiscence as well from the radial incisions. So, in an RK patient, depending on his correction and corneal thickness, I'll create anywhere from a 130- to 140-µm flap.

"The second thing that needs to be done is make a large-diameter flap," Dr. Will continues. "So, I'll typically do at least an 8.8-mm flap, with maybe a 4-percent elliptical oversize. You also have to change your laser's settings. Your sidewall energy in particular needs to go up at least 10, maybe 15 or even 20 percent. This is because the most difficult part about lifting a LASIK flap is that, when you cut the sidewall in these patients, the old radial incisions don't tend to cut as well, and that's when you get in trouble. Also, I use a 90-degree sidewall, vertical straight up and down, which gives a better chance of not getting ingrowth."

In addition to altering the side-cut energy, surgeons also have to modify their spot-line separation for creating the flap, Dr. Will says. "Typically, we use 5 µm for our spot-line separation," he says. "But for previous RK patients, I'll decrease that to 3 µm. So, you're making your sidewall spot separation and your layer separation closer together—you're at 3 µm between spots and 3 µm between layers. Again, this is for the purpose of getting a very clean sidewall. For the raster energy, if I'm using a 60-kHz laser, I pretty much always use a double-raster cut. If I'm using the iFS, I may leave the energy the same as in a typical case, or possibly bump it up by 10 percent at most."

In rare cases, you may need to do an enhancement later. "In these cases, you usually can't relift the flap easily more than a month postop," Dr. Will says. "When you try to lift the sidewall, it will be so fused after the previous incisions that you won't be able to lift it easily and will end up tearing the radial incisions apart. The thing to do on an enhancement is decrease the diameter of the flap by about 0.2 mm and recut the sidewall. So, if your original flap were 8.8 mm wide, you'd use 8.6 mm the second time. As for thickness, if I cut 130 µm on the original, I tend to go back and cut 150 µm on a recut to make sure I transect the old raster bed."

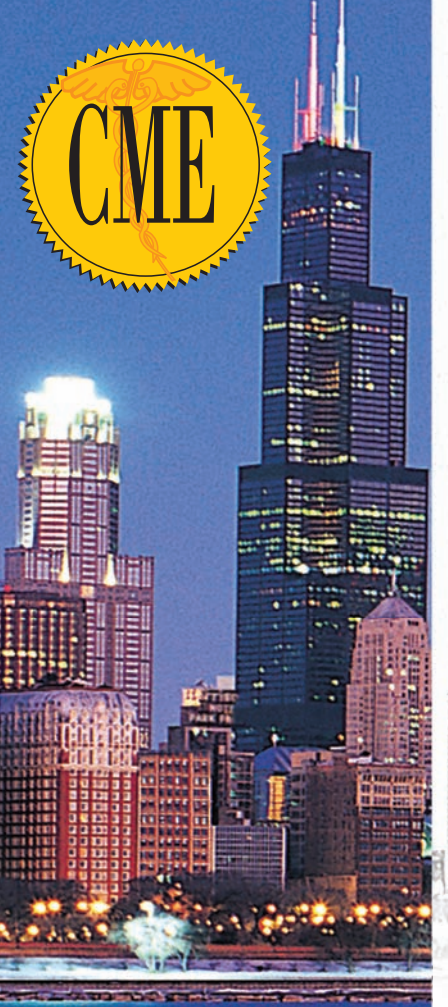
Rheumatoid Arthritis

Surgeons say patients with RA have eyes that usually don't respond the same way as the typical refractive surgery patient.

"RA is an auto-immune disease, and patients with auto-immune diseases can have unexpected wound healing issues," says Dr. Yoo. "So, as a broad statement, I'd say RA patients aren't good candidates for LVC. Also, if they are on antimetabolites for their disease, they aren't ideal candidates for LVC because the medication can alter the wound healing response.

"That being said, there might be special circumstances where patients may have a compelling reason for having LVC," Dr. Yoo adds. "For instance, a patient who is anisometropic and can't tolerate spectacles because of the difference between the eyes and can't wear contact lenses because his rheumatoid disease gives him difficulty in handling the contact lenses could be a candidate. If the RA is quiescent and doesn't require medication for control, that might be a patient in whom you say, 'OK, with your circumstances, let's see if you can handle LVC.' Dry eye would be my number-one concern in these patients, so I'd do a careful tear-film assessment: tear-film breakup time; Schirmer's to see if she's producing tears adequately; and fluorescein staining to look for any punctate keratopathy. If there are issues, or he's just subjectively symptomatic, I treat aggressively with artificial tears and potentially with punctal occlusion and topical cyclosporine-a. I also make sure he doesn't have any exposure that can be contributing to the dry eye."

Dr. Pascucci also won't operate on an RA patient whose disease isn't well-controlled. But for the ones on whom he will perform LVC, he takes an aggressive dry-eye treatment approach. "In non-RA patients, I tend to very generously lubricate the cornea with non-preserved artificial tears following LASIK, and sometimes add gels at bedtime," he avers. "I then step up therapy if it appears to be necessary, possibly going to plugs next and then maybe to Restasis after that. In an RA patient, though, I might pull out all the stops. I would plan on plugging him at the conclusion of the procedure and talk to him about the potential benefits of Restasis. If I felt Restasis was warranted, I might start it a week preop to see if we could somehow minimize the dry eye that develops. This type of patient—dry-eye wise—needs a full-court press from the get-go." REVIEW



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Eyelid Laxity and Obesity in Keratoconus

Doctors from the State University of New York, Buffalo, investigated the association between keratoconus and floppy eyelid syndrome, as well as obesity, obstructive sleep apnea and keratoconus, finding that keratoconus patients have an increased laxity to their eyelids, along with a more rubbery tarsus. This may be along the spectrum of floppy eyelid syndrome. Keratoconus patients also have a high prevalence of obesity and OSA, the latter an association that carries an increased risk of death from any cause, as well as stroke.

A prospective, case-controlled study of keratoconus patients with age-, sex-, race- and body mass index-matched controls was conducted at the Ross Eye Institute in Buffalo, with 15 patients enrolled in each group. Extensive eyelid laxity measurements were performed on both groups. Complete medical/ophthalmic histories and Epworth Sleepiness Scales were completed on 50 keratoconus patients and compared to the normal population.

Increased eyelid measurements of the vertical lid pull (p=0.001), lower lid pull (p=0.005), medial canthal tendon distraction (p=0.04) and palpebral width (p=0.01) were found in the keratoconus group compared with the matched control group. A more rubbery tarsus (p=0.03), increased corneal diameter (p=0.02) and increased exophthalmometry measurements (p=0.01) were also found. The prevalence of OSA (24 percent, n=24) and of obesity (52 percent, n=26) were higher in the keratoconus patients than the normal population.

Cornea 2013;32:1232-1236.
Pihlblad M, Schaefer D.

Outcomes That Influence CXL in Keratoconus and Ectasia

New Jersey doctors looked at the characteristics influencing outcomes of corneal cross-linking for keratoconus and ectasia, finding that patients with worse preoperative corrected distance visual acuity and higher topography-derived maximum keratometry values, particularly with a CDVA of 20/40 or a maximum K of 55 D or more, were most likely to have improvement after corneal cross-linking. No preoperative characteristics were predictive of CXL failure.

Corneal cross-linking was performed at a cornea and refractive surgery practice in eyes with keratoconus (n=66) or corneal ectasia (n=38). Multiple regression and odds ratio analyses were performed to determine independent predictors of changes in maximum K and CDVA one year postop. Preoperative characteristics included sex, age, uncorrected distance visual acuity, CDVA, maximum keratometry, corneal thickness, corneal haze, disease group and cone location. Postoperative improvement in maximum K was defined as flattening of 2 D or more and worsening as steepening of 1 D or more. Improvement in CDVA was defined as a gain of two lines or more, and worsening as a loss of one line or more.

Eyes with a preoperative CDVA of 20/40 or worse were 5.9 times (95 percent CI, 2.2 to 6.4) more likely to improve two or more Snellen lines. Eyes with a maximum K of 55 D or more were 5.4 times (95 percent CI, 2.1 to 14) more likely to have topographic flattening of 2 D or more. No preoperative characteristics significantly predicted worsening of visual acuity or corneal topography.

J Cataract Refract Surg 2013;39: 1133-1140.
Greenstein S, Hersh P.

Besifloxacin Associated with Delayed Epithelial Closure

Researchers from Massachusetts report an observation that photorefractive keratectomy patients treated with besifloxacin 0.6% on the stromal bed exhibited significant problems with corneal epithelial healing and delayed visual recovery.

These conclusions were drawn from a retrospective chart review of four patients (seven eyes) in an office-based private practice. The healing parameters examined included epithelial healing time, haze formation,

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discomfort and visual recovery. These patients were treated with besifloxacin 0.6% under bandage contact lenses placed after PRK was performed.

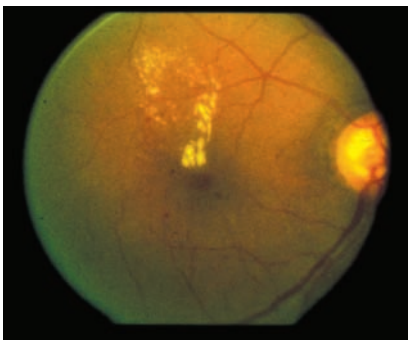
All the eyes had delayed epithelial closure (mean 8.8 days, r: five to 13 days), and all patients experienced a delayed visual recovery and significant pain after surgery. Two of the four patients experienced recurrent corneal erosions for weeks to months after undergoing PRK. All but one eye developed corneal haze persisting for a year or more after the surgery. Only one eye among the seven treated with besifloxacin 0.6% under BCL had 20/20 or better uncorrected visual acuity three months postop.

Cornea 2013;32:1365-1368.
Talamo J, Hatch K, Woodcock E.

Bevacizumab vs. Ranibizumab For the Management of DME

A prospective, randomized trial to compare visual acuity and spectral-domain optical coherence tomography outcomes associated with intravitreal bevacizumab vs. intravitreal ranibizumab for the management of diabetic macular edema has determined that both drugs are associated with similar effects on central subfield thickness through one year of follow-up. Intravitreal ranibizumab is associated with greater improvement in best-corrected visual acuity at some study visits and the mean number of injections is higher in the intravitreal bevacizumab group.

Forty-eight patients (63 eyes) with center-involved DME were randomly assigned to receive 1.5 mg (0.06 cc) intravitreal bevacizumab or 0.5 mg (0.05 cc) intravitreal ranibizumab at baseline and monthly if central subfield thickness was greater than 275 µm. Of these, 45 patients (60 eyes) completed 48 weeks of follow-up. At baseline, mean ± standard error BCVA (logMAR) was 0.60 (20/80) ±0.05 in the intravitreal bevacizumab group and 0.63 (20/80) ±0.05 in the intravitreal ranibizumab group. A significant improvement in mean BCVA was observed in both groups at all study visits ($p<0.05$); this improvement was significantly greater in the intravitreal ranibizumab group compared with the intravitreal bevacizumab group at weeks eight ($p=0.032$) and 32 ($p=0.042$). A significant reduction in mean central subfield thickness was observed in both groups at all study visits compared with baseline ($p<0.05$), with no significant difference in the magnitude of macular thickness reduction between groups. The mean number of injections was significantly higher ($p=0.005$) in the intravitreal bevacizumab group (9.84) than in the intravitreal ranibizumab group (7.67).


Diabetic macular edema responds well to both bevacizumab and ranibizumab.

Am J Ophthalmol 2013;156:502-510.
Nepomuceno A, Takaki E, Paes de Almeida F, Peroni R.

Socioeconomic Disparity and U.S. Adult Use of Eye-Care Services

Data from the United States National Health Interview Survey (2002 and 2008) shows that use of eye-care services in adults with self-reported age-related eye disease (AMD, cataracts, diabetic retinopathy or glaucoma) is significantly impacted by both poverty-income ratio and education levels.

National Institute on Minority Health and Health Disparities researchers used a cross-sectional, nationally representative sample of adults, including participants in the 2002 (n=3,586) and the 2008 (n=3,104) National Health Interview Survey who were at least 40 years of age and reported any age-related eye disease. A multiple logistic regression estimated predictive margins and the slope of index inequality measured the relationship between socioeconomic position (SEP) and use of eye-care services across the entire distributions of poverty-income ratio (PIR) and educational attainment.

In 2002, persons with ARED and a PIR of less than 1.5 were significantly less likely than those with a PIR of at least 5.0 to report visiting an eye-care provider (62.7 percent vs. 80.1 percent, $p<0.001$) or undergoing a dilated eye examination in the past 12 months (64.3 percent vs. 80.4 percent; $p<0.001$), after adjustment for other factors. Similarly, persons with less than a high school education were less likely than those with at least a college education to report a visit to an eye-care provider (62.9 percent vs. 80.8 percent, $p<0.001$) or dilated eye examination (64.8 percent vs. 81.4 percent, $p<0.001$). In 2002, the slope index of inequality showed statistically significant differences for eye-care provider visits across the levels of education (24.4 percent, $p=0.006$) and in 2008, it showed a significant difference for eye-care provider visits across levels of educational attainment (25.2 percent, $p=0.049$) and PIR (21.8 percent, $p=0.01$).

JAMA Ophthalmol 2013;131: 1198-1206.
Zhang X, Beckles G, Chou C, Saaddine J, et al.

MMC Unnecessary to Prevent Haze in Higher Myopia Post-PRK

In a double-masked, randomized, prospective trial, United States Naval Medical Center researchers in San Diego evaluated the safety and efficacy of mitomycin-C 0.01% (0.1 mg/mL) in preventing haze formation af-

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ter wavefront-guided PRK for higher myopia at three exposures, concluding that MMC may not be needed to prevent haze after modern PRK with a four-month steroid taper.

Sixty-, 30- and 15-second exposures (n=10, 9 and 9, respectively) of MMC 0.01% were compared in wavefront-guided PRK for higher myopia. One eye received MMC (surgical sponge) and the other a placebo. All eyes received a four-month tapering postoperative topical steroid regimen. Endothelial cell densities, haze scores, high- and low-contrast acuities and manifest refraction were measured preoperatively and one, three, six and 12 months postoperatively. Outcomes were analyzed as repeated measures over time.

The mean preoperative manifest refraction spherical equivalent was -5.98 D (r: 4.4 to 8.0 D). No eye developed more than trace haze. There was a significant difference in haze scores between MMC-treated eyes and untreated eyes at one and three months (p=0.034) but no difference at six and 12 months. Endothelial cell densities decreased in the treated eyes and untreated eyes at all three exposures at one month but returned to baseline by six months There was no difference in acuities or refractions with or without MMC, and there was no clinically significant difference in haze formation between MMC eyes and control eyes at the concentration and exposure used.

J Cataract Refract Surg 2013;39: 1358-1365.
Hofmeister E, Bishop F, Kaupp S, Schallhorn S.

Comparing Oral FA to SD-OCT In Detecting Macular Edema

An international team of researchers evaluated the safety and efficacy of oral fluorescein angiography compared to spectral-domain optical coherence tomography in detecting macular edema, concluding that oral FA is both safe and adequate. They found that oral FA is more sensitive than SD-OCT in detecting ME in cases of retinovascular diseases, but can fail to detect ME in cases of macular holes. To obtain a comprehensive evaluation of the presence of ME from different pathologies, a noninvasive examination with simultaneous oral FA and SD-OCT should be considered, the investigators advise.

The researchers reviewed the results of imaging studies for 1,928 eyes of 1,019 patients who had simultaneously undergone both oral FA and SD-OCT by a confocal laser ophthalmoscope. They determined the sensitivity in detecting ME, the discrepancy rate and kappa agreement for both techniques and with the eyes stratified by disease and diagnosis.

No allergic reactions occurred after oral FA. Mild gastric discomfort was noted in less than 1 percent of patients, while 1,840 eyes (95.4 percent) showed concordance between the two techniques; the kappa agreement was 90.3 percent. For ME, oral FA showed an overall sensitivity of 0.97 and SD-OCT an overall sensitivity of 0.91. Equivalent sensitivity was found in cases of wet age-related macular degeneration (0.99). Detection of ME by SD-OCT was significantly higher in cases of intense leakage on oral FA (p<0.001).

Retina 2013;33:1574-1583.
Barteselli G, Chihablani J, Lee S, Wang H, et al.

Prediction of AMD in the General Population

Using data from population-based studies, the Three Continent AMD Consortium (3CC) has developed a prediction model for late AMD. The 3CC state that its model is robust and distinguishes well between those who will develop late AMD and those who will not.

Three population-based studies (the Rotterdam Study, the Beaver Dam Eye Study and the Blue Mountains Eye Study) followed participants (n=10,106) with gradable fundus photographs, genotype data and follow-up data who did not have late AMD at baseline measurements. The features of AMD were graded on fundus photographs using the 3CC AMD severity sale. Associations with known genetic and environmental risk factors were tested using Cox proportional hazard analysis. In the Rotterdam study, the prediction of AMD was estimated for multivariate models by area under receiver operating characteristic curves. The best model was validated in the Beaver Dam Eye Study and the Blue Mountains Eye Study; associations of variables were re-estimated in the pooled data set. Beta coefficients were used to construct a risk score, and risk of incident of late AMD was calculated using Cox proportional hazard analysis. Cumulative risks were estimated used Kaplan-Meier product-limit analysis, and incident late AMD was determined per visit during a median follow-up period of 11.1 years with a total of four to five visits.

Overall, 363 participants developed late AMD; 3,378 participants developed early AMD; and 6,365 participants remained free of any AMD. The highest AUC was achieved with a model including age; sex; 26 nucleotide polymorphisms in AMD risk genes; smoking; body mass index; and baseline AMD phenotype. The AUC of this model was 0.88 in the Rotterdam Study; 0.85 in the Beaver Dam Eye Study and Blue Mountains Eye Study at validation; and 0.87 in the pooled analysis. Individuals with low-risk scores had a hazard ratio of 0.02 (95 percent CI, 0.01 to 0.04) to develop late AMD and individuals with high-risk scores had an HR of 22 (95 percent CI, 15.2 to 31.8). Cumulative risk of late AMD ranged from virtually none to more than 65 percent, for those with the highest risk scores.

Am J Ophthalmol 2013 doi:10.1016/j.ophtha.2013.07.053.
Buitendijk G, Rochtchina E, Myers C, van Duijn C, et al.

Two New Programs From Topcon Medical

Topcon Medical Systems' new CV-5000S Online Training Program for its CV-5000S Automated Refraction System is the first in a series of interactive, online product training systems. It shows CV-5000S users how to conduct a refraction, breaking it down into small, user-friendly learning modules. Through a combination of narrated video, graphics and step-by-step instructions, the system highlights the key features of the product and the operating procedures associated with each one. Users are also shown how to create customized refraction programs with the CV-5000S.

The system will be available 24/7 on the Topcon website to registered users, allowing them to access it at any time and from any location. This value-added feature of the CV-5000S will not only enhance the customers' experience but also make the refraction process a smooth and effortless procedure for both patient and operator. For information, visit topconmedical.com/products/cv5000s.htm.

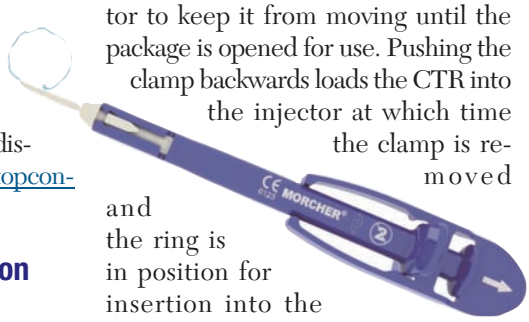
Topcon has also debuted its new Laser Trade-in Program for retinal laser users. The program will allow users of single-spot lasers to trade in their existing units for a new Pascal Synthesis or Streamline Green or Yellow Pattern Scanning Laser.

The new Pascal Synthesis is Topcon's premiere dual-port pattern scanning retinal laser, available in both 532-nm and 577-nm wavelengths. The compact, portable design of Synthesis allows it to integrate with Topcon SL-D7 and Haag-Streit-style slit lamps, with pricing similar to a premium single-spot laser system. Synthesis will allow fast and effective treatment of retinal disorders using clinically proven Pascal technology, while offering physicians the option of keeping their current slit-lamp setup. The Pascal or Pattern Scanning Laser method applies an innovative pattern scanning technology that allows the practitioner the use of a short duration pulse laser combined with a selection of delivery patterns that are automatically placed on the treatment area in less than a second, minimizing tissue damage and patient discomfort. For information, visit topconmedical.com/lasers.

Henderson Capsular Tension Ring Now Preloaded

FCI Ophthalmics reports that the Henderson Capsular Tension Ring from Morcher is now also available preloaded on a disposable injector identified as the EyeJet, Type 10C.

Each preloaded injector is packaged in a sterilized, peel-open, contoured container. The units come with one of the CTRs already affixed to the hook of the injector with a clamp on the injector to keep it from moving until the package is opened for use. Pushing the clamp backwards loads the CTR into the injector at which time the clamp is removed and the ring is in position for insertion into the capsular bag.



The Henderson Ring (designed by

This article has no commercial sponsorship.

Dr. Bonnie Henderson of Ophthalmic Consultants of Boston) is an open C-shaped loop made of a single piece of polymethyl methacrylate that has enhanced flexibility and resistance to breakage. The ring performs the same basic function as standard CTRs by stabilizing the capsular bag before, during and after cataract surgery.

The ring features eight equally spaced indentations spanning its circumference and creating a sinusoidal shape. The indentations allow for easier nuclear and cortical material removal while still maintaining the desired stretch of the capsular bag.

Approved for marketing in the United States, the Henderson EyeJet is available only from FCI Ophthalmics. For information, call 1 (800) 932-4202; e-mail info@fci-ophthalmics.com or fax 1 (781) 826-9062.

Accutome Offers Keeler Eye-Care Products to U.S. Customers

Accutome has partnered with Keeler to offer Keeler's portable slit lamps, the PSL Classic and PSL One, and the Keeler Applanation Tonometer in the United States.

The PSL Classic allows eye-care professionals to deliver an eye exam in non-ambulatory patient visits, off-site clinics and exams of young children and patients who don't fit into the traditional examination lane, as well as for veterinary use on animals of all sizes. The PSL Classic's advanced optics offer x10 and x16 "flip lever" magnification, with illumination control down to zero. Its backup facility ensures power 100 percent of the time. The PSL slit and wheels include slits from 0.15 to 1.6 mm wide, a 12-mm circle, and a 1-mm square to produce anterior flare, aiding in the diagnosis of uveitis.

The PSL One offers one standard magnification of 10x and is a more cost-effective option than Keeler's PSL Classic. The PSL One also features slit and wheels from 0.15 to 1.6 mm, a 12-mm circle and a 1-mm square. Its precision-machined aluminum chassis creates a sturdy structure able to withstand daily travel and use in a busy practice. Both the PSL Classic and the PSL One can be utilized with an iPhone adaptor that enables ophthalmic video capture, turning the devices into instant digital slit lamps with high-resolution video.

Accutome will also sell the Keeler Applanation Tonometer, an FDA-approved contact tonometer that aids glaucoma diagnosis with intraocular pressure measurements at the slit lamp as part of routine examinations. The KAT uses the Goldmann method, calculating the force required to flatten a constant area of the cornea using a special prism mounted on the tonometer head and placed against the cornea. KAT is compatible with most slit lamps.

For more information on the products, call Accutome at 1(800) 979-2020, visit accutome.com or e-mail info@accutome.com.

Argus II Designated as New Tech; Payment Approved

Second Sight Medical Products announced that the Argus II Retinal Prosthesis System was approved by the Centers for Medicare & Medicaid Services for a new technology add-on payment (inpatient setting of care) and a transitional pass- through payment (outpatient setting of care) beginning October 1, 2013. These payments are designed to support timely access to innovative technologies for Medicare beneficiaries. According to the CMS, cases involving the Argus II System that are eligible for new technology add-on payments under the Medicare Inpatient Prospective Payment System will be identified by a new ICD-9-CM procedure code: 14.81.

Additionally, CMS has established a transitional pass-through payment for Argus II. This payment will be available to all hospital outpatient facilities and ambulatory surgical centers that perform this procedure for Medicare beneficiaries, and will be identified by the 0100T CPT code. Guideline information on billing, coding and payment for hospital outpatient departments and ASCs was to be released by CMS in the October quarterly update.

Nidek and Marco Announce the New ARK-1s with Glare Testing

Nidek and Marco have introduced their newest autorefractor/autokeratometer, the ARK-1s, the only autorefractor/autokeratometer with glare testing. The ARK-1s measures objective spherical, cylindrical refractive errors and cylinder axis from the refractive status of the patient's eye. In addition, this is the first ARK that combines the capability of glare testing with low-contrast testing, accommodation, retro-illumination, visual acuity chart presentation and the ability to subjectively refine the sphere.

The glare testing capability makes it easier to test patients with cataracts. Traditional methods can be cumbersome and time-consuming with questionable accuracy, the

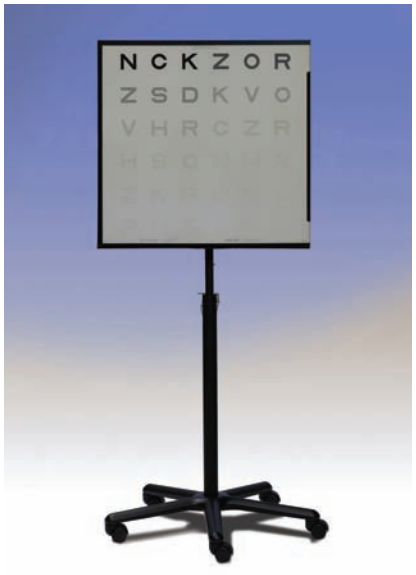
company says. For doctors who also use low-contrast testing for their patients, the ARK-1s has the capability.

The accommodative measurement helps doctors to detect problems in pre-presbyopia, latent hyperopes, and children who have trouble reading. The retro-illumination modality helps to educate patients, with an actual image of their cataract progression.

This all-in-one compact design has Nidek/Marco's auto alignment EyeTracking System on the X-Y-Z axis for consistent, accurate readings. For information, call 1 (800) 874-5274 or visit marco.com.

Contrast Sensitivity Testing for AMD, Other Retinal Diseases

VectorVision has introduced a new letter contrast sensitivity test for the evaluation of patients with AMD or other retinal diseases. The new ELCT (Evans Letter Contrast Test)



provides a range of contrast sensitivity levels using a letter size which was designed specifically for evaluating the stabilization or improvements in vision of AMD patients following treatment. This scientifically developed design allows eye care practitioners to test patients with AMD and other retinal diseases in a standardized and comprehensive way.

The ELCT is used in conjunction with the VectorVision/Good-lite ESV-3000, an LED-based, auto-calibrated, back-lighting system that ensures uniform and consistent lighting for testing each patient.

For information, visit vectorvision.com.

B + L Updates PreserVision AREDS2 Formula Vitamin

Bausch + Lomb introduced its new PreserVision AREDS 2 Formula eye vitamin and mineral supplement, the only commercially available supplement in the United States that exactly matches the updated formula based on the latest clinical evidence from the National Eye Institute AREDS2 study.

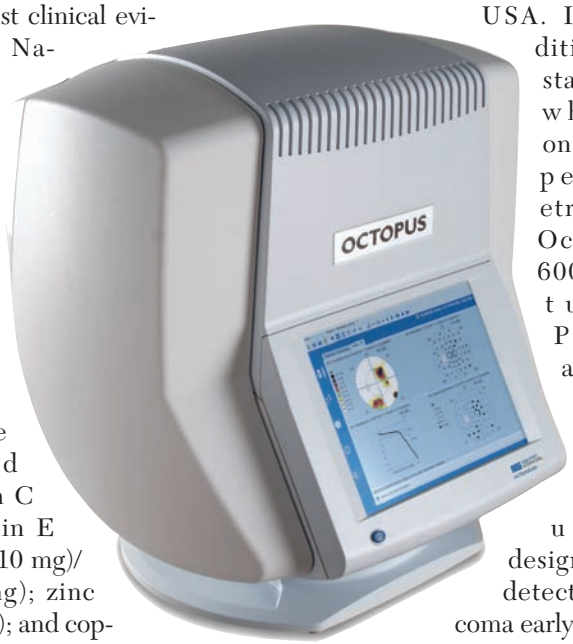
The daily dose (two soft gels) of new PreserVision AREDS 2 Formula provides the same levels of all six clinically proven nutrients as the NEI-supported formula: vitamin C (500 mg); vitamin E (400 IU); lutein (10 mg)/zeaxanthin (2 mg); zinc (80 mg zinc oxide); and copper (2 mg cupric oxide). The combination of these nutrients at the specific levels recommended by the NEI is only available from Bausch + Lomb.

Bausch + Lomb originally introduced a PreserVision AREDS 2 Formula that included lutein, zeaxanthin and 1,000 mg of omega-3 fatty acids in 2010, reflecting existing evidence of potential benefit for these nutrients that also formed the rationale for the AREDS2 protocol. When the AREDS2 findings were published, Bausch + Lomb confirmed its intention to reformulate PreserVision AREDS 2 to match the updated recommendation as quickly as possible. The reformulated product began shipping to wholesalers in the United States in late July, less than three months from the release of the AREDS2 data.

For more information, visit bausch.com.

Haag-Streit: New Member of The Octopus Family

The new Octopus 600 perimeter combines early detection and progression monitoring of glaucoma into one compact unit, says Haag-Streit USA. In addition to standard white-on-white perimetry, the Octopus 600 features Pulsar, a patented flicker stimulus designed to detect glaucoma early.



The Octopus 600 features an ergonomic design with a minimal footprint. Large trial lenses, built-in correction for presbyopia and a newly reconfigured response button are designed for a more comfortable patient experience. The perimeter operates via touchscreen, keyboard or mouse and will function as a stand-alone unit or as part of a network. For information, visit haag-streit-usa.com. REVIEW

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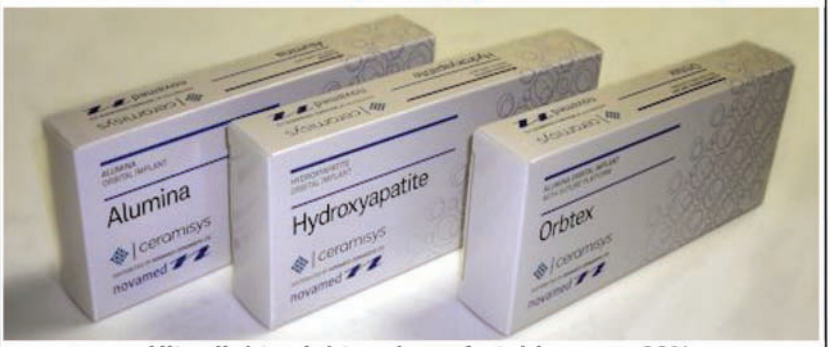

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'Pulsating bubbles' in his peripheral vision and vision loss prompt a patient's referral to Wills' Neuro-ophthalmology and Retina Services.

Murtaza Adam, MD

Presentation

A 59-year-old Caucasian male was referred to the Wills Neuro-ophthalmology Service for a six-month history of intermittent bilateral visual disturbances and two-week history of painless vision loss in the left eye. He described his visual disturbances as yellow and blue pulsating bubbles in the peripheral vision of both eyes. Approximately one month prior to presentation, the patient reported that his vision was measured to be 20/25 in each eye by his optometrist. He denied any headache, fevers/chills, weight loss, jaw claudication, diplopia or other neurologic symptoms.

Medical History

The patient's past ocular history was significant for mild cataracts in both eyes. His past medical history was significant for coronary artery disease status post quadruple bypass, hypertension, hyperlipidemia, osteoarthritis and hepatitis C. His medications included simvastatin, lisinopril, carvedilol and ibuprofen. He denied any recent travel and had no pets at home. Social history was negative for high-risk sexual activity and illicit drug use. He endorsed a 45 pack-year smoking history and a history of heavy alcohol use until eight months ago.

Examination

The patient's corrected visual acuity was 20/40 in the right eye and 20/400 in the left without improvement on pinhole. Color plates were full in the right eye and significantly decreased in the left. Amsler grid testing revealed a paracentral inferior scotoma in the left eye. Pupils were normal with no afferent pupillary defect. Motility was full in both eyes. He denied diplopia in all directions of gaze. Intraocular pressure was within normal range and equal in both eyes. There was no proptosis. Nuclear sclerotic lens changes were present. His fundoscopic exam revealed mild hypertensive changes in both eyes and retinal pigment epithelium changes in the left macula. Neurologic exam was unremarkable without weakness, paresthesias, loss of reflexes or ataxia.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 130

Diagnosis, Workup and Treatment

The patient underwent 24-2 Humphrey visual field testing which revealed scattered peripheral defects in the right eye and a dense inferior defect in the left eye, confirming Amsler testing. Optical coherence tomography disclosed borderline optic nerve retinal nerve fiber layer thickening in the superior quadrants bilaterally and mild disruption of RPE and photoreceptor layers of the central macula in the left eye. No subretinal fluid or cystic changes were evident at that time. An MRI of the brain and orbits demonstrated old cerebellar infarcts and was negative for any acute ischemic changes, masses or inflammatory lesions.

In the context of his macular findings on OCT, the patient was referred to the Retina Service for further evaluation. In the two-week interval between visits, the patient's vision worsened from 20/40 to 20/80 in the right eye and improved from 20/400 to 20/40 in the left eye. A juxtapapillary Hollenhorst plaque and cotton wool spot without retinal whitening was noted in the right eye. The following day, the patient was admitted by his cardiologist for a previously scheduled coronary angiography for symptoms of worsening angina. Angiography revealed complete blockage of two coronary grafts not amenable to endovascular stenting, and carotid Doppler ultrasound was negative for significant carotid stenosis.

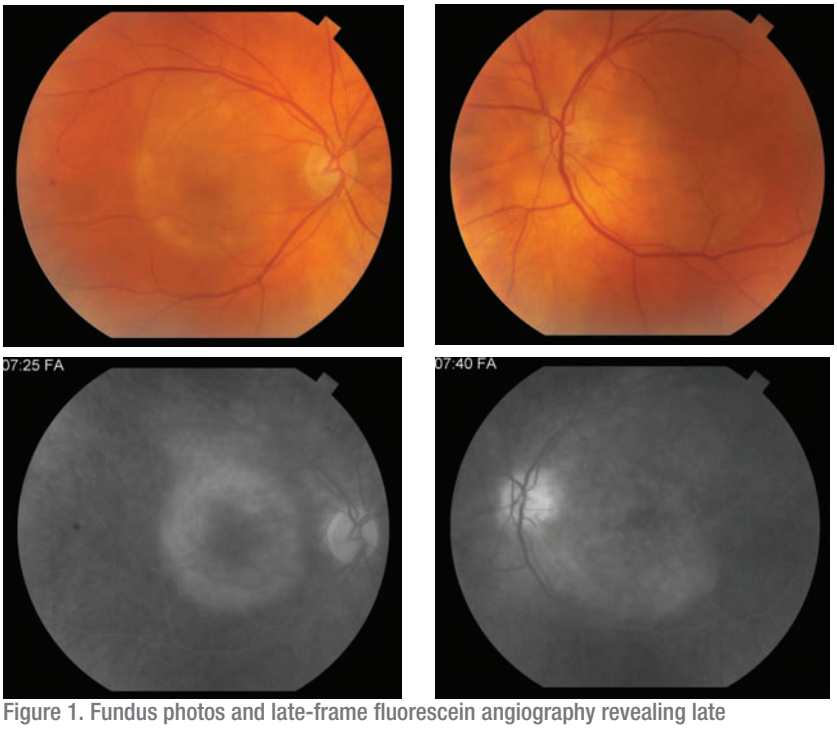

Figure 1. Fundus photos and late-frame fluorescein angiography revealing late hyperfluorescence in the areas of placoid chorioretinal infiltration.

The patient was lost to follow up for one month following his admission for coronary angiography and over this interval his vision painlessly declined to count fingers in each eye. Re-examination at the slit lamp showed new findings of +1 anterior chamber cell and + 2 vitreous cell. Funduscopy now revealed yellow, creamy, indistinct chorioretinal infiltrates localized to both maculae and fluorescein angiography disclosed leakage of both discs and late hyperfluorescence in the areas of chorioretinal infiltration *(See Figure 1)*. OCT demonstrated disruption of the inner segment ellipsoid band, nodular RPE changes, and submacular fluid in the left eye *(See Figure 2)*.

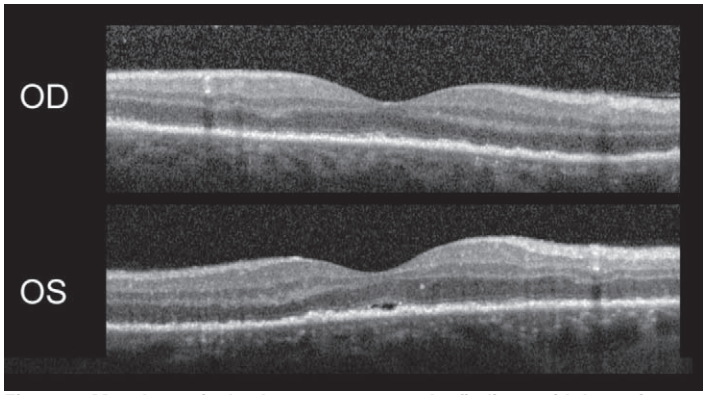

Figure 2. Macular optical coherence tomography findings with loss of outer retinal architecture and trace submacular fluid in the left eye.

That day, the patient was admitted to the Ophthalmology Service for further workup and treatment. Erythrocyte sedimentation rate and C-reactive protein were both elevated, to 110 and 1.1, respectively. Pulsed IV steroids were empirically initiated. Given the patient's negative review of systems, a broad, extensive workup was obtained to investigate potential diagnoses including sarcoidosis; rheumatoid arthritis; systemic lupus erythematosus; HIV; syphilis; Lyme disease; Wegener's granulomatosis; polyarteritis nodosa; and monoclonal gammopathies.

After two days of treatment with IV methylprednisolone, the patient's vision improved to 20/200 in the right eye and 20/30 in the left eye. His hospital course was complicated by transiently uncontrolled hypertension and an episode of angina for which se-

rial troponins were negative. He was discharged on 80 mg of oral prednisone daily with instructions to follow up with the Retina Service. Prior to this follow-up, his treating physician was notified that his workup yielded positive rapid plasma reagin (RPR) and fluorescent treponemal antibody absorption (FTA-ABS) reactivity consistent with syphilis infection. Human immunodeficiency virus testing was negative. The patient was subsequently re-admitted for two weeks of treatment with intravenous penicillin. Following this treatment course, his macular edema and subretinal fluid resolved and vision substantially improved to 20/25 in each eye.

Discussion

As Sir William Osler said, "He who knows syphilis knows medicine."[1] Known as the "great mimicker," the sexually transmitted spirochete *Treponema pallidum* can clinically declare itself in any organ system, not uncommonly leading clinicians down a false diagnostic pathway before the actual diagnosis is known.[2] It is estimated that there are approximately 12 million new cases of syphilis annually, 90 percent of which occur in developing countries.[3] Between 1990 and 2000, the annual rate of primary and secondary syphilis in the United States declined 87 percent to its lowest recorded level.[4] However, in 2004 the rate of syphilis resurged 28 percent, primarily in men.[5] In more recent years, younger men and men who have sex with men (in which rates of HIV infection are higher) have accounted for 67 percent of all syphilis cases in the United States.[6]

Acquired syphilis is conventionally divided into four stages. Primary stage is characterized by a painless chancre at the site of inoculation two to six weeks after infection.[7] Secondary syphilis manifests 10 weeks following infection with non-specific symptoms of malaise and fatigue as well as a disseminated rash involving the palms and soles. Latent syphilis is clinically undetectable and can last for decades until the onset of tertiary syphilis, which is characterized by highly morbid cardiovascular and neurologic manifestations.

Ocular syphilis is an uncommon manifestation of the disease, but is often instructive of the underlying diagnosis. Accounting for approximately 4 percent of all cases of uveitis,[8] syphilitic uveitis may manifest at any stage of disease, occurring in 2.5 to 5 percent of patients with tertiary syphilis.[7] Although posterior uveitis is the most common way for ocular syphilis to present, a large variety of presenting signs have been described in both HIV-positive and HIV-negative patients, including keratitis; gummous iris nodules; focal retinitis; multifocal choroiditis; phlebitis; arteritis; papillitis; and serous and exudative retinal detachments.[6,7,9]

Our case is consistent with the distinct clinical entity acute syphilitic posterior placoid chorioretinitis (ASPPC). First described by J. Donald Gass, MD, in 1990, ASPPC is caused by large, placoid, yellowish lesions at the level of the pigment epithelium in the macula and juxtapapillary areas.[10] Patients with ASPPC tend to have concomitant HIV infection and, in a recent series, nearly 60 percent of patients had bilateral involvement.[11] On fluorescein angiography, early central hypofluorescence is typically noted prior to late hyperflourescence in the affected macula.[12] Leakage at the disc can also be noted. OCT findings have been more recently described and include disruption of the inner segment ellipsoid band, nodular thickening of the RPE with loss of the linear outer segment/RPE junction, and occasionally, loss of the external limiting membrane, accumulation of subretinal fluid and punctate hyperreflectivity in the choroid.[11]

The crux of diagnosing ocular syphilis is serologic testing. Given the association with non-granulomatous uveitis, it has been recommended that syphilis serological testing be obtained even in the absence of suggesting clinical findings.[13] Serologic diagnosis relies upon both treponemal and non-treponemal testing.[7,9] Non-treponemal tests including the Venereal Disease Laboratory Report (VDRL) and RPR card test have utility in screening for active disease and antibody quantification to gauge therapeutic response. Treponemal tests such as the FTA-ABS test are used for confirmation of prior or current infection. Lumbar puncture for cerebrospinal fluid analysis is indicated in patients with ocular syphilis as it can detect subclinical neurologic involvement and can thus be predictive of morbidity and mortality.[14] In cases where serologic testing is unreliable, such as with patients with collagen vascular disease, advanced age, or HIV infection, direct treponeme visualization with dark-field microscopy or polymerase chain reaction-based analysis of intraocular fluids can be performed.[15,16] Any patient with confirmed syphilis should be also tested for HIV, as risk factors for both diseases are similar and the presence of a chancre greatly increases risk of acquiring or transmitting the disease.[7]

Acquired syphilis with ocular involvement should be treated as neurosyphilis with intravenous penicillin G 3 to 4 million units daily for 10 to 14 days.[17] Although alternative treatments with ceftriaxone and azithro-

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mycin have been proposed in patients with a penicillin allergy, there is limited evidence to guide dosing and duration of treatment.[7] Thus, penicillin-desensitization is recommended in these patients.[17]

In the case described, the patient's atypical presentation led clinicians down multiple diagnostic pathways before the underlying diagnosis of syphilis was revealed. Reflecting the indolent course of his disease, it was not until two months after the initial presentation that the patient demonstrated any signs of ocular inflammation (anterior, posterior and chorioretinal). Abrupt changes in vision and an elevated ESR prompted immediate empiric treatment with intravenous steroids. Ultimately, serologic testing confirmed the diagnosis of ASPPC and the patient was successfully treated with intravenous penicillin.

The key to timely, accurate diagnosis of ocular syphilis is a high level of clinical suspicion, which is confirmed with serologic testing. In this case, the indolent course with bilateral involvement, delayed presence of ophthalmic inflammation and ultimately positive serology alerted the treating physicians to the possibility of ocular syphilis. REVIEW

The author would like to thank Nicolas Biro, MD, of the Neuro-ophthalmology Service and Rajiv Shah, MD, and Carl Park, MD, of the Retina Service for their time and assistance in preparing this case report.

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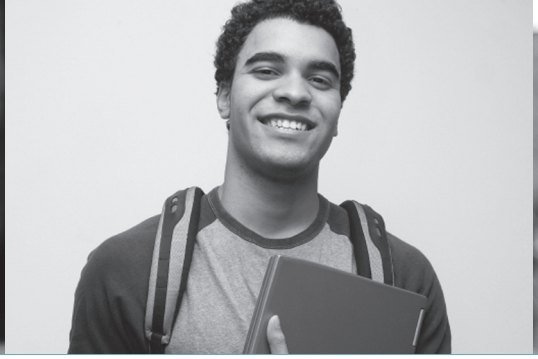


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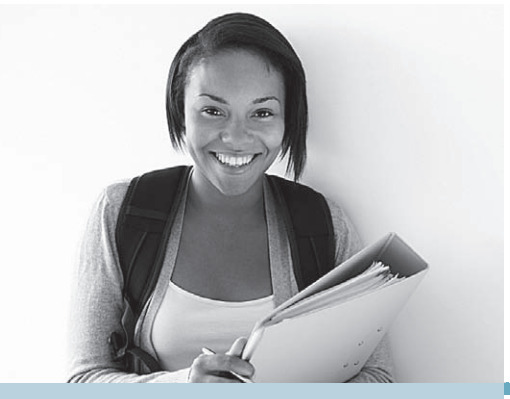

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INDICATIONS AND USAGE

LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Pigmentation: Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes: LUMIGAN® 0.01% and 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: LUMIGAN® 0.01% and 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% and 0.03% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory, or Neovascular Glaucoma: LUMIGAN® 0.01% and 0.03% has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

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

Use With Contact Lenses: Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% and 0.03% and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

Clinical Studies Experience: 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 rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical studies with bimatoprost ophthalmic solutions (0.01% or 0.03%) the most common adverse reaction was conjunctival hyperemia (range 25%–45%). Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia with 0.01% or 0.03% bimatoprost ophthalmic solutions. Other common reactions (>10%) included growth of eyelashes, and ocular pruritus.

Additional ocular adverse reactions (reported in 1 to 10% of patients) with bimatoprost ophthalmic solutions included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, conjunctival hemorrhage, and abnormal hair growth. Intraocular inflammation, reported as iritis, was reported in less than 1% of patients.

Systemic adverse reactions reported in approximately 10% of patients with bimatoprost ophthalmic solutions were infections (primarily colds and upper respiratory tract infections). Other systemic adverse reactions (reported in 1 to 5% of patients) included headaches, abnormal liver function tests, and asthenia.

Postmarketing Experience: The following reactions have been identified during postmarketing use of **LUMIGAN®** 0.01% and 0.03% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **LUMIGAN®** or a combination of these factors, include: dizziness, eyelid edema, hypertension, nausea, and periorbital and lid changes associated with a deepening of the eyelid sulcus.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C

Teratogenic effects: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether **LUMIGAN®** 0.01% and 0.03% is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** is administered to a nursing woman.

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

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

Hepatic Impairment: In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.03% for a 10 kg child.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

PATIENT COUNSELING INFORMATION

Potential for Pigmentation: Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution).

Potential for Eyelash Changes: Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** 0.01% and 0.03%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container: Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice: Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **LUMIGAN®** 0.01% and 0.03%.

Use with Contact Lenses: Patients should be advised that **LUMIGAN®** 0.01% and 0.03% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration.

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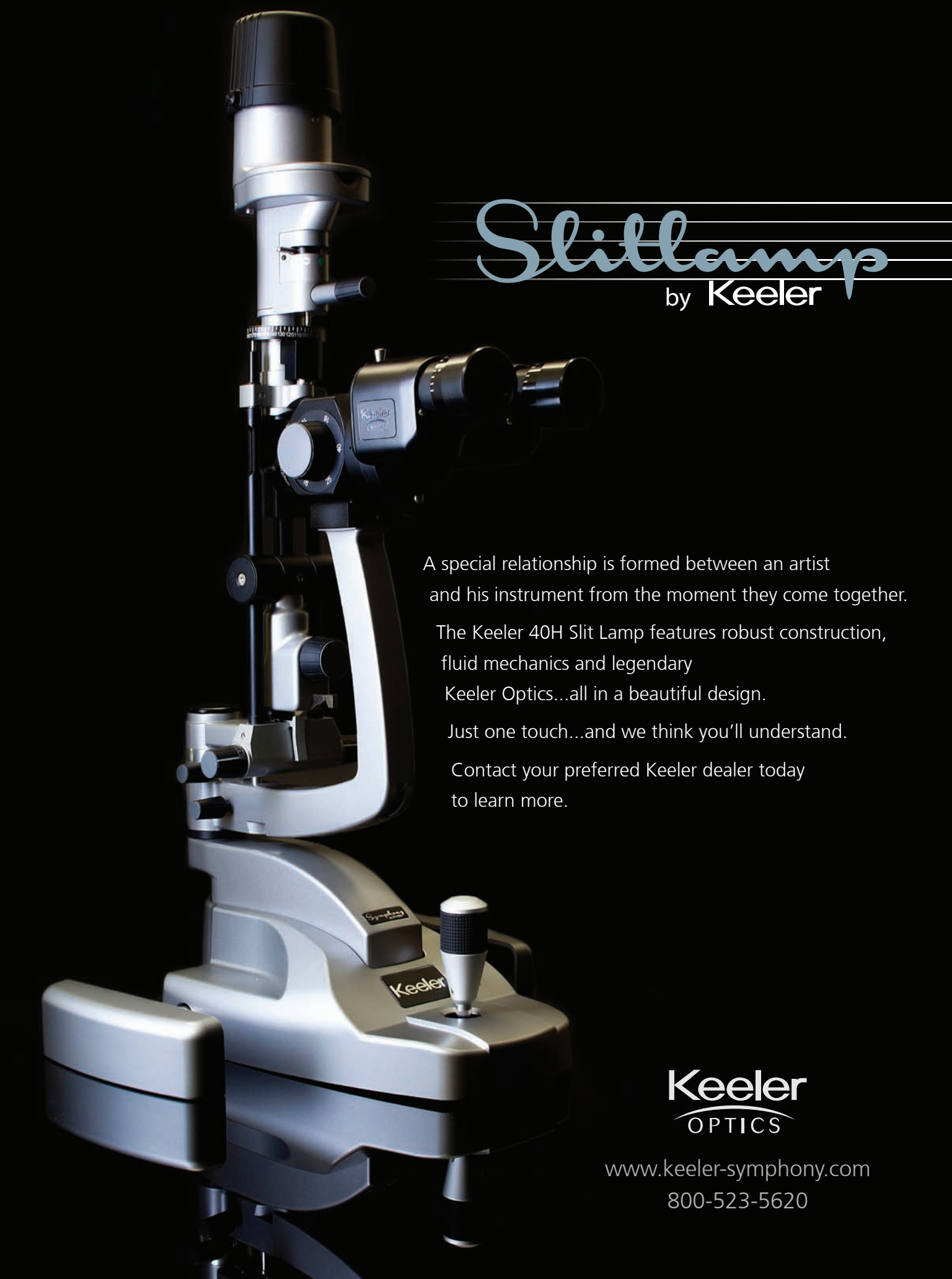
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LUMIGAN® should be used with caution in patients with active intraocular inflammation (eg, uveitis) because the inflammation may be exacerbated. Macular edema, including cystoid macular edema, has been reported with LUMIGAN®. LUMIGAN® should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Adverse Reactions: The most common (25%-45%) adverse event with LUMIGAN® was conjunctival hyperemia. Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia. Other common events (> 10%) included growth of eyelashes and ocular pruritus.

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