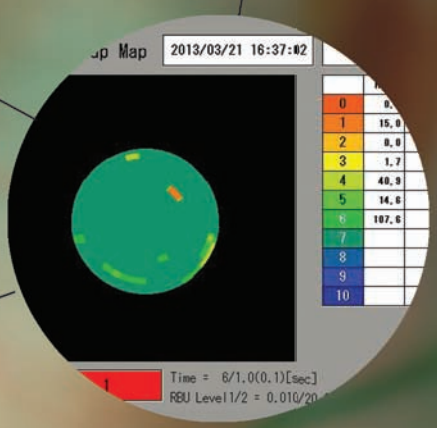
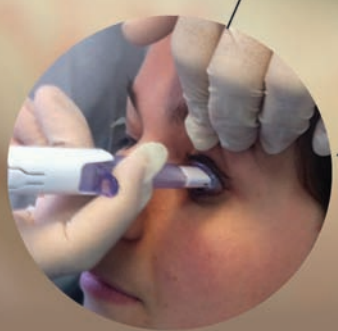
REVIEW of Ophthalmology

October 2013 • revophth.com

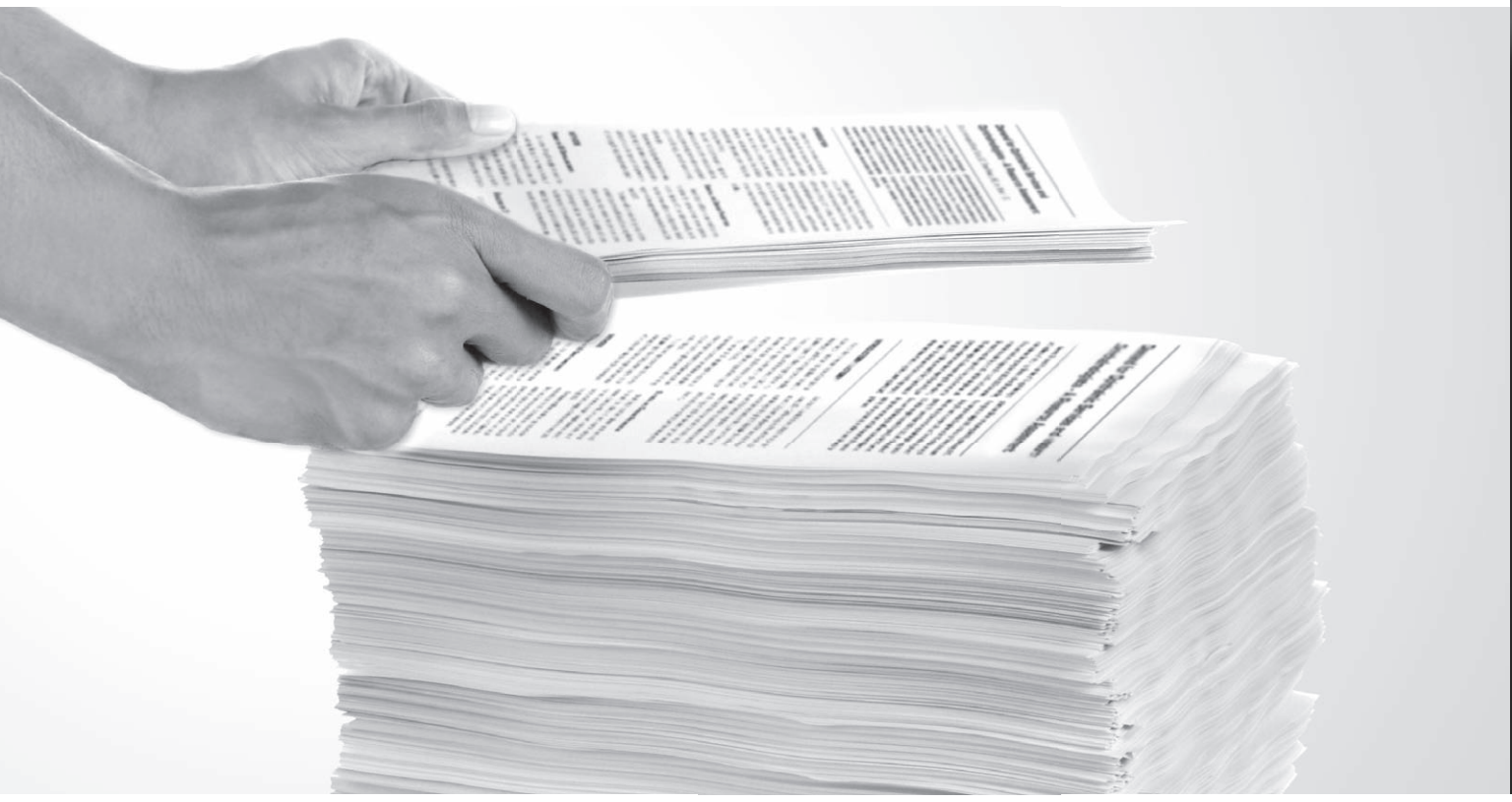
Dry-Eye Issue





jmi

Toric outcomes:
The evidence is overwhelming



Measuring Up to Today's Surgical Standards

The IOLMaster® has been used extensively in peer-reviewed, published studies of toric IOL implantation.[1] In these studies, excellent surgical outcomes were reported using IOLMaster keratometry measurements.

Visit www.IOLMaster.info/toricstudies to review the summary of studies with reported refractive outcomes for toric IOLs.

Agreement with Manual Keratometry

The IOLMaster measures up to another important standard. Excellent agreement exists between the IOLMaster and manual keratometry for mean power, cylinder power and axis, with superior repeatability and reproducibility.[2]

With clinical evidence that is truly overwhelming, it's no wonder the IOLMaster is the preferred method of keratometry for toric IOL calculations.[3]

Visit us in New Orleans

Drop by AAO booth 1919 to learn how the IOLMaster can support your growing toric IOL practice.

[1] Bullimore MA, The IOLMaster and Determining Toric IOL Power, 2013
[2] Bullimore MA, Buehren T, Bissman W. Agreement between a partial coherence interferometer and 2 manual keratometers. J Cataract Refract Surg. 2013 Jul 19.
[3] Leaming DV, 2012 Practice Styles and Preferences of the U.S. ASCRS Members Survey

Carl Zeiss Meditec, Inc. 800 342 9821 www.meditec.zeiss.com/us

ZEISS

We make it visible.

REVIEW NEWS
Volume XX • No. 10 • October 2013

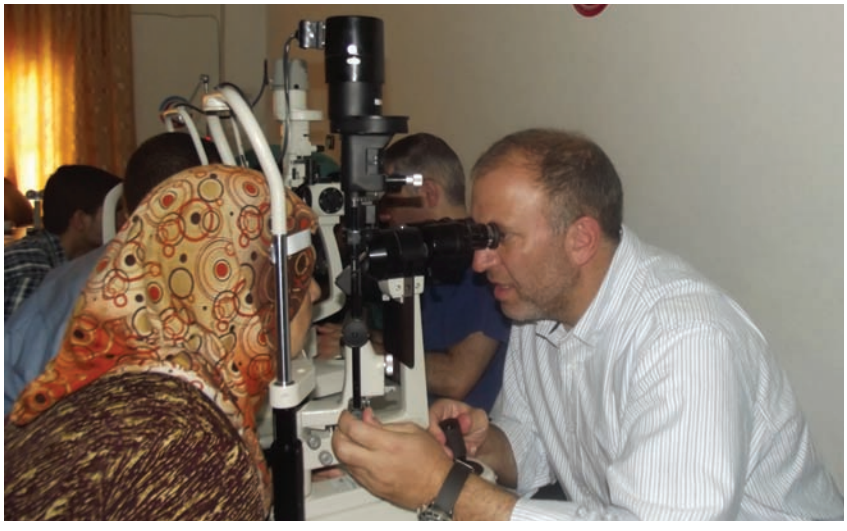
Florida Surgeon Hopes to Fill Acute Need for Eye Care in Syria

As the confrontation over the use of nerve gas dominates the headlines, civil strife in Syria has captured the world's attention. Out of the spotlight, a Syrian-American ophthalmologist from Pensacola, Fla., has been working with colleagues and aid groups on site to provide eye-care services to the country's devastated populace.

Raised in Syria, with his residency and fellowship in the United States, retina specialist Aref Rifai, MD, has been concentrating his efforts near Aleppo in the country's northern section, and offers it as an example of the need: "Aleppo is a city of 2.5 million people and used to have about 2,000 physicians," says Dr. Rifai. "Today, there are fewer than 100, and probably fewer than 10 ophthalmologists covering the entire city."

Dr. Rafai is a member of the Syrian American Medical Society, and set about through SAMS and other aid groups to equip three hospitals in the rural north near the border with Turkey with ophthalmic equipment. For his first shipment, he was able to collect $70,000 to purchase a vitrectomy machine, a laser, a microscope and some ancillary equipment. Working with colleagues from the United States and the UK, Dr. Rafai now has about 10 to 12 surgeons who make week-long rotations every two or three months to supplement the efforts of local Syrian ophthalmologists.

"A lot of the injuries are ruptured globes or patients who have shrapnel in their eyes that require surgery," he says. "On my last visit, I did 17 or 18 surgeries in four days, working around the clock one day" on both routine and injury-related retinal cases.



Pensacola, Fla., retina specialist Aref Rifai providing eye-care services in his native Syria. His group is accepting donations of used ophthalmic equipment to equip hospitals there.

SAMS is set up to accept both used medical and surgical equipment, and financial donations as well. Information on the group is available at sams-use.net. In addition to medical care, SAMS is involved in humanitarian efforts to restore decimated rural villages with the means to support themselves, such as a project to donate cows to farming areas. Another group providing relief and humanitarian services to Syria is savingfamiles.org.

Even when the immediate crisis is resolved, Dr. Rafai expects a long process before the needs of the Syrian people are met. "The infrastructure has taken a tremendous hit," he says. "I'd estimate that 30 percent of the population is internally displaced; they don't have a home to go to."

Gene Variant Tied to AMD

An international team of researchers, led by scientists at the Genome Institute at Washington University School of Medicine in St. Louis and the University of Michigan School of Public Health in Ann Arbor, has identified a gene mutation linked to age-related macular degeneration.

It's not the first gene variation linked to AMD, but it is the first to suggest a mechanism where the variant may contribute to the disease. The researchers report that a change in the C3 gene, which plays a role in inflammation and in the body's immune response, also

contributes to macular degeneration. The study was published online Sept. 15 in *Nature Genetics*.

"In past studies of AMD, there is a clear relationship between the complement pathway and the onset of this disease," said co-senior investigator Elaine R. Mardis, PhD. "The complement system is part of the immune system that helps amplify or 'complement' the efforts of immune cells to fight infections. So the idea is that the gene variant interferes with the complement pathway's normal function throughout life, and that can damage the retina over time, which ultimately leads to AMD's emergence."

The researchers sequenced DNA from 10 regions of the genome that had been linked to AMD in previous genetic studies. They analyzed a total of 57 genes in 2,335 patients with macular degeneration. Then the researchers sequenced the same genes in 789 people of the same age who did not have AMD.

The search turned up two gene variants: one in the C3 complement gene, and an alteration that had been identified in previous studies of macular degeneration.

"Finding the variant that had been identified previously helped confirm that we were on the right track," explained Dr. Mardis, a professor of genetics and co-director of the Genome Institute. "And it's likely this new variant was discovered because of the very large number of patients whose DNA we sequenced. By analyzing so many AMD patients, it was possible to find variants that may not have been identified in a smaller patient sample and to establish that this C3 gene variant is unique to people with AMD."

The two gene variants together contribute to a threefold increased risk for macular degeneration. Dr. Mardis and her co-investigators hypothesize that the mutations work

in tandem to increase AMD risk by interfering with the inactivation of complement in the retina.

"When you have these mutations, interactions between the proteins that cascade in the complement pathway are altered," Mardis said. "And when they're altered, the secondary response to infection, which involves complement, also is altered. So our hypothesis is that over time, because of the role of the complement pathway in the retina, damage begins to accrue, and eventually that leads to vision loss."

The next step is to look at additional DNA regions in the more than 2,000 patients and controls who were involved in this study. The researchers will broaden their look across the genome and go beyond the 10 DNA regions analyzed in this study.

"We hope to identify new genes, perhaps more genes in the complement pathway, perhaps genes in other inflammatory response pathways, or in areas we wouldn't have anticipated finding any genes related to AMD," she said. "We're taking a wide look at the genome to see what turns up."

Impaired Autophagy Tied to AMD

A new study published in the *PLoS One* journal challenges conventional wisdom on the pathogenesis of age-related macular degeneration. The researchers found that degenerative changes and loss of vision are caused by impaired function of the lysosomal cleanup mechanism, or autophagy, in the fundus. The results open new avenues for the treatment of dry AMD, which currently lacks an efficient treatment. The University of Eastern Finland played a leading role in the study, which also involved research groups from Italy, Germany and Hungary.

AMD is a storage disease in which harmful protein accumulations develop behind the retina. These accumulations are indicative of the severity of the disease. As the disease progresses, retinal sensory cells in the central vision area are damaged, leading to loss of central vision. The cell biological mechanisms underlying protein accumulations remain largely unknown.

This is the first time that impaired lysosomal autophagy, which renders the cells in the fundus unable to dispose of old, deformed or otherwise faulty proteins, has been implicated in AMD, the researchers say. Drugs inhibiting the impairment of autophagy could possibly even stop the progression of AMD.

Cataract Surgery Cuts Mortality Risk

People with cataract-related vision loss who have had cataract surgery to improve their sight are living longer than those with visual impairment who chose not to have the procedure, according to an Australian cohort study published in September's *Ophthalmology*. After comparing the two groups, the researchers found a 40-percent lower long-term mortality risk in those who had the surgery.

The research data was gathered in the Blue Mountains Eye Study. A total of 354 persons aged 49 years and older and diagnosed with cataract-related vision impairment – some of whom had undergone surgery and others who had not – were assessed between 1992 and 2007. Adjustments were made for age and gender as well as a number of mortality risk factors, including hypertension, diabetes, smoking, cardiovascular disease, body mass index and measures of frailty and comorbid disease. Follow-up visits took place five and 10 years after the baseline exam.

Previous research had indicated that older persons with visual impairment were likely to have greater mortality risk than their age peers with normal vision, and that cataract surgery might reduce this risk. These studies, unlike the Blue Mountains Eye Study, compared people who had undergone cataract surgery with those in the general population or with those who had not had cataract surgery, and did not link vision status to the surgical status.

"Our finding complements the previously documented associations between visual impairment and increased mortality among older persons," said Jie Jin Wang, PhD, of the Westmead Millennium Institute and one of lead researchers of the study. "It suggests to ophthalmologists that correcting cataract patients' visual impairment in their daily practice results in improved outcomes beyond that of the eye and vision, and has important impacts on general health."

The association between correction of cataract-related visual impairment and reduced mortality risk is not clearly understood, but plausible factors may include improvements in physical and emotional well-being, optimism, greater confidence associated with independent living after vision improvement, as well as greater ability to comply with prescription medications.

One limitation of the study is that participants with cataract-related visual impairment who did not have cataract surgery could have had other health problems that prevented them from undergoing surgery, and that these other health problems could partly explain the poorer survival among non-surgical participants. This issue is addressed by the researchers in a subsequent study.

Knowing the osmolarity of your patient's tears is essential

The Gold Standard for the diagnosis and management of Dry Eye Disease.

TearLab™

www.tearlab.com

CLIA WAIVED
Reimbursed at $45.42/patient
by Medicare under the Laboratory Fee Schedule - CPT 83861 QW*

CE | FDA 510(k) Cleared (k083184) | CPT is a copyright and registered trademark of the American Medical Association (AMA). *Please consult Medicare payment rules for your area; this is not an official guide on all matters pertaining to reimbursement. | 920132 REV C

First Animal Model to Simulate Graves' Disease

Researchers have developed the first animal model simulating the eye complications associated with the thyroid condition Graves' disease, a breakthrough that could pave the way for better treatments, according to a recent study accepted for publication in the Endocrine Society's journal *Endocrinology*.

Graves' disease is an autoimmune disorder that causes the body to produce antibodies that attack the thyroid gland. The condition causes the thyroid gland to become overactive and produce too much thyroid hormone. About 1 percent of Caucasian women have autoimmune thyroid disease where the thyroid is either over- or underactive. Among those who have Graves' disease, more than half develop eye complications, according to the study's lead author, J. Paul Banga, PhD, of King's College London School of Medicine in the United Kingdom. These complications include Graves' orbitopathy, where swelling of tissue behind the eyes causes them to bulge outward. The condition can cause pain and lead to blindness.

"Current treatment options for eye complications associated with Graves' disease are limited," Dr. Banga said. "Better treatments are needed for Graves' orbitopathy to reduce the risks of permanent disfigurement and social stigma. Having an animal model to test preventative treatments could lead to important advances that will ultimately benefit people with Graves' disease."

The condition is currently treated with steroids, which can cause undesirable side effects such as weight gain and osteoporosis.

Though researchers have previously developed animal models of Graves' disease, these were challenging to replicate and none were able to simulate the eye problems seen in people with Graves' disease.

To develop the new model, researchers injected mice with small, circular, double-stranded DNA molecules called plasmids. Over the course of three months, scientists used electronic pulses to ensure the DNA molecules were absorbed into the cells of each mouse. Mice that underwent this procedure developed eye problems like those seen in human patients who have Graves' disease, while the control group of mice did not develop these complications.

"The new animal model opens the door for scientists to conduct needed mechanistic studies and identify preventative therapies to minimize this painful and debilitating condition," Dr. Banga said. REVIEW

To the Editor:

I read "When Plastics Issues Complicate Cataract Surgery" (July 2013), and this article is certainly of interest, especially regarding both postoperative ptosis, as well as lower lid problems that may follow an otherwise uncomplicated cataract procedure.

Entropion following a cataract procedure has also been reported[1] and, although infrequent, it should be discussed as a possible postoperative occurrence which might require surgical correction.

In many ways, postoperative entropion is analogous to the more commonly developing postoperative ptosis,[1] and advancement or re-attachment of the capsulopalpebral fascia to repair this is analogous to repair of the dis-inserted or thinning of the levator aponeurosis for upper lid repair.

Feldstein describes a three-suture technique,[2] and indeed advancing the dehisced retractor may stabilize the inferior tarsal border from rotating forward, thereby correcting the entropion, just as advancing the thinned or disinserted levator aponeurosis may solve postoperative ptosis—since they are analagous structures.

Involutional entropion has several contributing causes,[3] one of which is dis-insertion of the capsulopapebral fascia from the inferior tarsal border followed by pre-septal orbicularis moving upward to override the pre-tarsal orbicularis,[4] resulting in entropion. Although usually not associated with any inciting ocular irritation, cataract surgery has indeed been reported to directly precede, and likely to have contributed, to the postoperative entropion in a number of reported cases.

This possibility of postoperative entropion that might need surgical correction, reported by a number of sources, should therefore be discussed with the prospective cataract patient along with discussion of the other conditions thoroughly noted in your article. Preoperative findings of horizontal lower lid laxity, another predisposing cause for entropion, might make this discussion a priority even in an individual with good lower lid position.

Stuart M. Terman, MD
Solon, Ohio 44139

1. Levine MR, Enlow MK, Terman SM. Spastic Entropion After Cataract Surgery Ann Ophthalmology 1992:24:195-198.
2. Feldstein M. A method of surgical correction of entropion in aged persons. Ear Nose Throat J 1960:39:730-731.
3. Levine MR. Involutional entropion. Geriatric Ophthamology 1986:1:14-21.
4. Jones CT. The anatomy of the lower eyelid and the cause and cure of entropion. Am J Ophthalmol 1960:49:29-36.

EyePromise® EZ Tears™

Rapid Dry Eye Relief – Guaranteed.

EyePromise EZ Tears™ 30-Day Dry Eye Relief Guarantee

EyePromise EZ Tears relieves the symptoms of dry eye fast by improving tear composition and reducing inflammation.*

Visit **eyepromise.com/samples** or contact our customer support team at **866.833.2800** today to receive **FREE EZ Tears samples!**

highest quality NATURAL Ingredients

DOCTOR RECOMMENDED

NSF

Made in the USA

www.eyepromise.com | support@eyepromise.com

*These statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.

REVIEW Editorial Board

Contributors

Advisory Board

Jobson Professional Publications Group

BUSINESS OFFICES
11 CAMPUS BOULEVARD, SUITE 100
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
SALES MANAGER, NORTHEAST,
MID ATLANTIC, OHIO
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

SALES MANAGER, SOUTHEAST, WEST
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

VICE PRESIDENT OF OPERATIONS
CASEY FOSTER
(610) 492-1007 CFOSTER@JOBSON.COM

MANAGER EDUCATIONAL CONFERENCES/MEETINGS
MEG McDONALD
(610) 492-1045 MMCDONALD@JOBSON.COM

PRODUCTION MANAGER
SCOTT TOBIN
(610) 492-1011 STOBIN@JOBSON.COM

SUBSCRIPTIONS
$63 A YEAR, $99 (U.S.) IN CANADA,
$158 (U.S.) IN ALL OTHER COUNTRIES.
SUBSCRIPTIONS E-MAIL: **RHSUBS@HALLDATA.COM**
CIRCULATION E-MAIL: **RHSUBS@HALLDATA.COM**

CIRCULATION
PO BOX 2026, SKOKIE, IL 60076
(877) 529-1746
OUTSIDE USA: (847)763-9630
FAX: (847)763-9631

SENIOR CIRCULATION MANAGER
ANTHONY GUADAGNINO
(212) 219-7870 aguadagnino@jobson.com

CHIEF OPERATING OFFICER
JEFF MACDONALD

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, HUMAN RESOURCES
LORRAINE ORLANDO

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

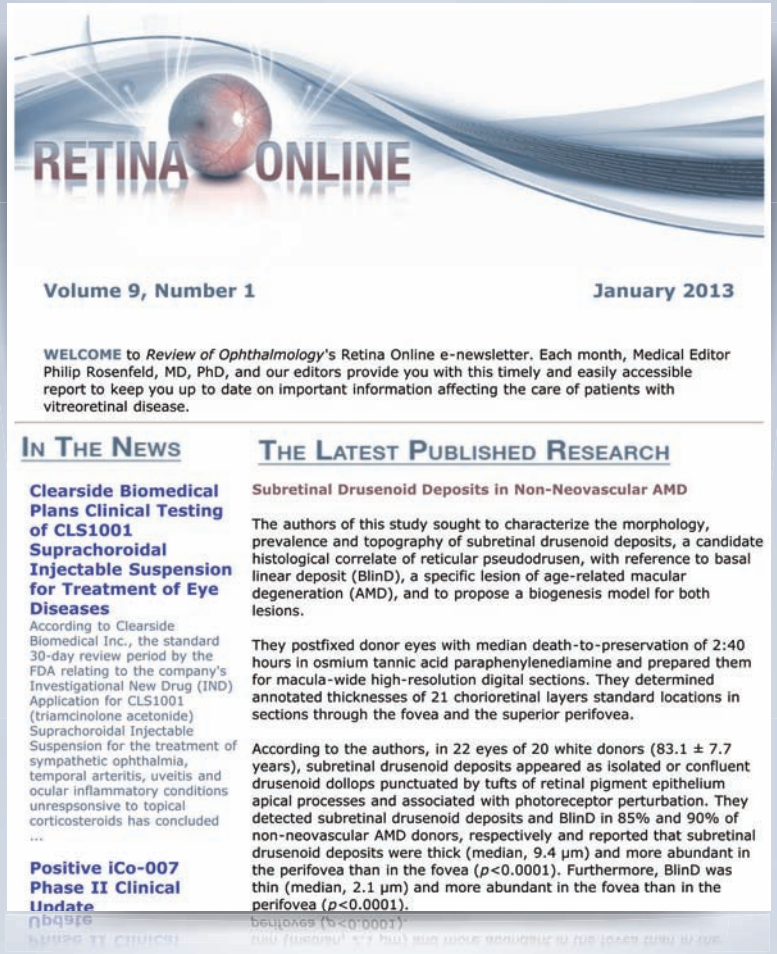
VICE PRESIDENT, CIRCULATION
EMELDA BAREA

jmi

100 Avenue of the Americas
New York, NY 10013

REVIEW OF OPHTHALMOLOGY (ISSN 1081-0226; USPS No. 0012-345) is published monthly, 12 times per year by Jobson Medical Information. 100 Avenue of the Americas, New York, NY 10013-1678. Periodicals postage paid at New York, NY and additional mailing offices. Postmaster: Send address changes to Review of Ophthalmology, PO Box 2026, Skokie, IL 60076, USA. Subscription Prices: US One Year $63.00, US Two Year $112.00, Canada One Year $99.00, Canada Two Year $181.00, Int'l One Year $158.00, Int'l Two Year $274.00. For subscription information call (877) 529-1746 (USA only); outside USA, call (847) 763-9631. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.V

RETINA ONLINE
E-NEWSLETTER



RETINA ONLINE

Volume 9, Number 1 January 2013

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

IN THE NEWS

Clearside Biomedical Plans Clinical Testing of CLS1001 Suprachoroidal Injectable Suspension for Treatment of Eye Diseases

According to Clearside Biomedical Inc., the standard 30-day review period by the FDA relating to the company's Investigational New Drug (IND) Application for CLS1001 (triamcinolone acetonide) Suprachoroidal Injectable Suspension for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unrespsonsive to topical corticosteroids has concluded ...

Positive iCo-007 Phase II Clinical Update

THE LATEST PUBLISHED RESEARCH

Subretinal Drusenoid Deposits in Non-Neovascular AMD

The authors of this study sought to characterize the morphology, prevalence and topography of subretinal drusenoid deposits, a candidate histological correlate of reticular pseudodrusen, with reference to basal linear deposit (BlinD), a specific lesion of age-related macular degeneration (AMD), and to propose a biogenesis model for both lesions.

They postfixed donor eyes with median death-to-preservation of 2:40 hours in osmium tannic acid paraphenylenediamine and prepared them for macula-wide high-resolution digital sections. They determined annotated thicknesses of 21 chorioretinal layers standard locations in sections through the fovea and the superior perifovea.

According to the authors, in 22 eyes of 20 white donors (83.1 ± 7.7 years), subretinal drusenoid deposits appeared as isolated or confluent drusenoid dollops punctuated by tufts of retinal pigment epithelium apical processes and associated with photoreceptor perturbation. They detected subretinal drusenoid deposits and BlinD in 85% and 90% of non-neovascular AMD donors, respectively and reported that subretinal drusenoid deposits were thick (median, 9.4 µm) and more abundant in the perifovea than in the fovea ($p<0.0001$). Furthermore, BlinD was thin (median, 2.1 µm) and more abundant in the fovea than in the perifovea ($p<0.0001$).

Once a month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with timely information and easily accessible reports that keep you up to date on important information affecting the care of patients with vitreoretinal disease.

3 EASY WAYS TO SUBSCRIBE!

http://www.jobson.com/globalemail/

Fax: 610.492.1039 or Call: 610.492.1027

REVIEW® of Ophthalmology

LET'S TALK SOLUTIONS

We understand the flexibility today's ophthalmic practices demand. That is why we offer products that can be transported from lane-to-lane or office-to-office and handle 100% of your patient load.

Accutome, Keeler, Volk
AAO Booth #2245
Three great companies combining to provide a wide array of products and the best customer experience.

PSL Classic
#29-1450

AccuPen® Handheld Tonometer #24-3000
PachPen® Handheld Tonometer #24-5100

www.accutome.com/product/psl-classic-portable-slit-lamp

ACCUTOME®
A HALMA COMPANY

3222 Phoenixville Pike, Malvern, PA 19355 USA • 800-979-2020 • 610-889-0200 • FAX 610-889-3233 • www.accutome.com

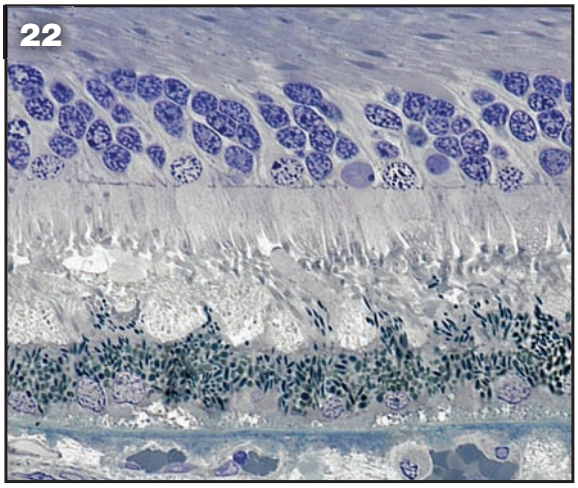
REVIEW® of Ophthalmology

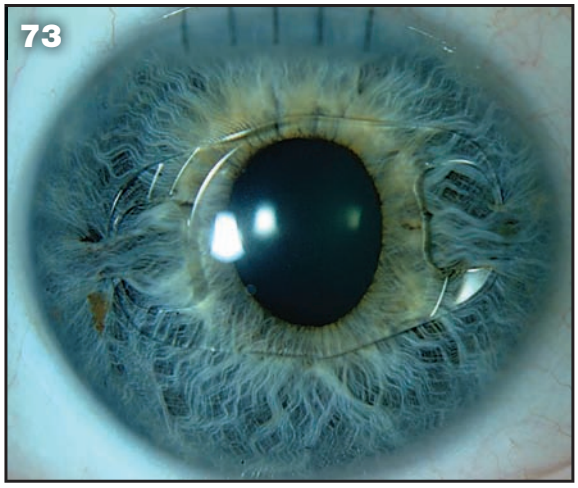
October 2013 • Volume XX No. 10 | revophth.com

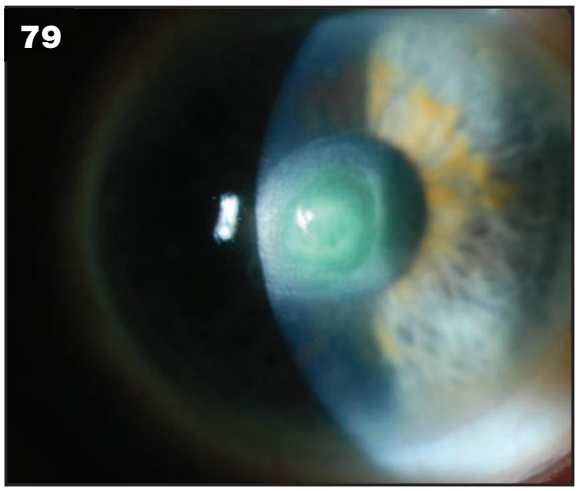
Cover Focus

Feature Article

Departments







Proof positive for more eyes

- Proven therapeutic utility in a variety of superficial ocular infections—including blepharitis, conjunctivitis, and others
- Profound activity against common gram-positive pathogens—Streptococci, Staphylococci,[1] and MRSA[2,3]
- A sensitivity and resistance profile that's remained virtually unchanged over time[4]
- Unsurpassed safety profile—allergenicity and side reactions are practically non-existent[1]
- Convenient dosing—1-3 times daily[1]
- Tier 1 co pay vs. leading brands[5]

Please see adjacent page for full prescribing information

Important Safety Information

Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic.

This product should not be used in patients with a history of hypersensitivity to Bacitracin.

www.ferapharma.com

References: 1. Bacitracin Ophthalmic Ointment [Package Insert]. Locust Valley, NY; Fera Pharmaceuticals, LLC;2009. **2.** Kowalski RP, Karenchak LM, Romanowski EG. Infectious disease: changing antibiotic susceptibility. *Ophthalmol Clin N Am* 2003;16:1-9. **3.** Freidlin J, Acharya N, Lietman TM, Cevallos V, Whitcher JP, Margolis TP. Spectrum of eye disease caused by methicillin-resistant *Staphylococcus aureus*. *Am J Ophthalmol* 2007;144:313-315. **4.** Recchia FM, Busbee BG, Pearlman RB, Carvalho-Recchia CA, Ho AC. Changing trends in the microbiologic aspects of postcataract endophthalmitis. *Arch Ophthalmol* 2005;123:341-346. **5.** http://fingertipformulary.com/drugs/Bacitracinopthalmicointment/

FERA™ PHARMACEUTICALS

BACITRACIN OPHTHALMIC OINTMENT USP
STERILE

℞ only

DESCRIPTION: Each gram of ointment contains 500 units of Bacitracin in a low melting special base containing White Petrolatum and Mineral Oil.

ACTION: The antibiotic, Bacitracin, exerts a profound action against many gram-positive pathogens, including the common Streptococci and Staphylococci. It is also destructive for certain gram-negative organisms. It is ineffective against fungi.

INDICATIONS: For the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

CONTRAINDICATIONS: This product should not be used in patients with a history of hypersensitivity to Bacitracin.

PRECAUTIONS: Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic. The prolonged use of antibiotic containing preparations may result in overgrowth of nonsusceptible organisms particularly fungi. If new infections develop during treatment appropriate antibiotic or chemotherapy should be instituted.

ADVERSE REACTIONS: Bacitracin has such a low incidence of allergenicity that for all practical purposes side reactions are practically non-existent. However, if such reaction should occur, therapy should be discontinued.

DOSAGE AND ADMINISTRATION: The ointment should be applied directly into the conjunctival sac 1 to 3 times daily. In blepharitis all scales and crusts should be carefully removed and the ointment then spread uniformly over the lid margins. Patients should be instructed to take appropriate measures to avoid gross contamination of the ointment when applying the ointment directly to the infected eye.

HOW SUPPLIED: 3.5 g (1/8 Oz) sterile tamper proof tubes, NDC 48102-007-35.

FERA

Manufactured for:
Fera Pharmaceuticals, LLC
Locust Valley, NY 11560
FPBC00N Rev. 08/09

REVIEW® of Ophthalmology

Convincing Your Partner to Participate

The word partnership has long been used to describe the relationship between physician and patient. In many cases, it's a stretch. The best-laid treatment plans rely on both partners performing as agreed and, in the real world, it just doesn't go as planned. It's been estimated in diabetes care, for example, that less than 60 percent of patients take 80 percent or more of their prescribed medications.

In glaucoma, even patients who remember to take their drops may be splashing more of them down their cheeks than reach their target. Given the multitude of issues that can derail medical management of glaucoma, it's not surprising that much of the research and literature on compliance has focused on drug delivery mechanisms, patient education, reduced dosing, and other factors outside of the clinic. This month, our Glaucoma Management department (p. 66) looks at a less widely discussed area of compliance—keeping follow-up visits. It's an interesting take on an issue that can greatly affect outcomes even in patients who follow their drug regimen.

One the key tenets of the new Affordable Care Act is taking physician/patient partnership into some uncharted territory. In an effort to increase patient engagement in their own care, meaningful use incentives are being offered to hospitals as well as certain eligible providers who can demonstrate that 5 percent of their patients are using their patient portal or EHR system to send secure electronic messages and enter data on their medical care. Certainly, they're not targeting the chronically ill such as glaucoma or diabetes patients. And if you had to today find 5 percent of your patient base that is eagerly involved in their care to this degree (to be clear—you don't) most doctors could.

But the concept of an incentive to drive this kind of patient engagement is established. There is, likewise, consideration of providing not just providers but patients with financial and other incentives in order to motivate healthy behaviors and improve their performance as medical "partners."

In the Deloitte 2013 Survey of U.S. Physicians, participants were asked for their perceptions about the types of incentives that might work best with consumers. "A majority of physicians (71 percent) believe that if consumer incentives were widely introduced, financial ones (e.g., direct payments, reduced insurance premiums or reduced co-pays) might work best with consumers in an attempt to motivate them to engage in healthy behaviors," the authors report. An equal number agree that "consumer incentives could be very helpful to achieve better treatment compliance."

The search for an engaged partner goes on.

Donna McCune, CCS-P, COE

Reimbursement Issues With Lasering Floaters

Most vitreous floaters do not require treatment, but for those that do, knowing the appropriate CPT codes is a necessity.

Q How are most patients who suffer with vitreous floaters treated?

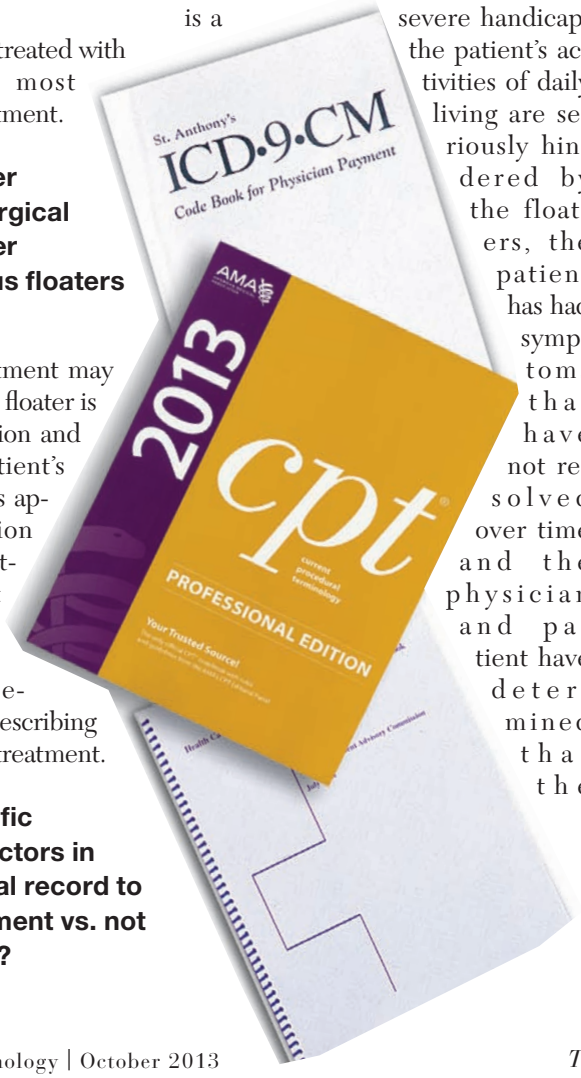
A Most patients are treated with reassurance, as most floaters require no treatment.

Q Are floaters ever treated with surgical intervention? Is laser treatment of vitreous floaters successful?

A Yes. Surgical treatment may have merit when a floater is significant, limiting vision and compromising the patient's ability to function. This approach is the exception and not the rule. Treatment may or may not be successful. A small number of articles exist, dating back to between 2002 and 2005, describing some success with this treatment.

Q Are there specific documented factors in the patient's medical record to support laser treatment vs. not treating with lasers?

A As with many ophthalmic surgical procedures, the medical record should indicate that there is a severe handicap, the patient's activities of daily living are seriously hindered by the floaters, the patient has had symptoms that have not resolved over time and the physician and patient have determined that the benefits of laser treatment outweigh the risk.



Q Will third-party payers cover laser treatment for vitreous floaters?

A Maybe. Unfortunately, very few coverage policies exist on this treatment. Some payers consider the treatment "investigational and experimental" and therefore it is not covered. It's best to confirm coverage before treatment.

Q Are there any CPT codes describing this treatment?

A Yes, actually. CPT code 67031 (*Severing of vitreous strands, vitreous face adhesions, sheets, membranes or opacities, laser surgery, one or more stages*) and 67299 (*Unlisted procedure, posterior segment*) both apply to lasering vitreous floaters. Use CPT 67031 when a visually significant opaque floater is severed from its attachment, allowing it to sink to the bottom of the vitreous and out of the line of sight. When a floater is vaporized by the YAG laser, rather than severed, CPT 67031 does not apply, so you would use CPT 67299 instead.

This article has no commercial sponsorship.

For patients starting or changing PGA therapy

Drop IOP.
Keep monotherapy.

Indication: LUMIGAN® (bimatoprost ophthalmic solution) 0.01% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Important Safety Information

Warnings and Precautions: LUMIGAN® causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® is administered. Iris color change may not be noticeable for several months to years. After discontinuation of bimatoprost, iris pigmentation is likely to be permanent, while eyelid and eyelash changes have been reported to be reversible in some patients. Patients should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

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.

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

Write it RIGHT 0.01%

LUMIGAN® 0.01%
(bimatoprost ophthalmic solution) 0.01%

LUMIGAN® 0.01% AND 0.03%
(bimatoprost ophthalmic solution)

Brief Summary—Please see the LUMIGAN® 0.01% and 0.03% package insert for full Prescribing Information.

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.

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

APC70EN12 based on 71807US13.

Rx only

ALLERGAN®

Q How frequently are these codes utilized? Will the frequent use of these codes attract attention from Medicare?

A These codes are rarely used. Medicare data from 2011, the most recent year available, indicates CPT 67031 was reimbursed 3,014 times; this number is actually lower than it has been in prior years. The unlisted CPT code 67299 was reimbursed 522 times in 2011, but remember that it applies to other procedures as well as lasering vitreous floaters.

It is worth noting that physicians who perform this procedure may attract unwanted attention from Medicare and other payers because they will be considered outliers and thus subject to extra scrutiny.

Q What is the Medicare reimbursement rate for the procedure coded with 67031? Is the physician reimbursed differently if the laser is performed in an ambulatory surgery center or hospital outpatient department?

A The national Medicare Physician Fee Schedule amount in 2013 for CPT 67031 is $401.81 if the procedure is performed in the office. If the procedure is performed in an ASC or HOPD, the physician will incur a site of service reduction. The 2013 national Medicare reimbursement rate for 67031 with the SOS reduction is $368.81.

Q Is there facility reimbursement for an ASC or HOPD in CPT code 67031?

A Yes. The national Medicare HOPD reimbursement is $410.79 in 2013. For ASCs, the 2013 national Medicare allowed amount is $230.51.

Q Can we expect similar reimbursement rates from other third-party payers?

A Possibly. In all cases, other third-party payers set their own rates, which may vary considerably from Medicare.

Physicians who perform this procedure may attract unwanted attention from Medicare; they will be considered outliers and thus subject to extra scrutiny.

Q Is there a postop period with CPT code 67031?

A Yes. This laser is considered a major procedure and carries a 90-day global period. All other rules associated with major procedures apply.

Q Are there challenges associated with the unlisted code 67299 if that code applies?

A Numerous challenges do exist with all unlisted codes, including 67299:

- There is no stipulated reimbursement schedule for physicians;
- Claims are evaluated and an appropriate payment rate is selected on a case-by-case basis;
- There is no published global period;
- HOPD reimbursement for CPT code 67299 is the same as for a YAG capsulotomy ($410.79);
- Within Medicare, unlisted codes are ineligible for ASC facility fee reimbursement;
- Each claim stands alone; reimbursement for one case does not set precedent for the next.

Q If coverage and reimbursement rates are uncertain, should we consider pre-authorization with third-party payers?

A If a payer permits pre-authorization, you should always secure it in writing. They may or may not be willing to reveal reimbursement rates but you can ask. Unfortunately, Medicare will not preauthorize.

Q If the patient has Medicare, how can we indemnify ourselves when coverage is uncertain?

A You can ask the patient to sign an Advance Beneficiary Notice of Noncoverage prior to treatment. By signing an ABN, the Medicare beneficiary acknowledges that he has been advised that Medicare will probably–or certainly–not pay. The beneficiary also agrees to be responsible for payment, either personally or through another insurance, including Medicaid.

Q If the patient has a commercial insurance, can we utilize an ABN in case insurance denies the claim?

A Yes. You can develop a financial waiver form similar to Medicare's ABN. This waiver informs the patient of potential financial liability and secures an agreement to pay for the service in the event of a denial. REVIEW

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


Better Outcomes Through Technology

A computer with an Internet connection can give you access to powerful tools for learning more about your results.

Walter Bethke, Managing Editor

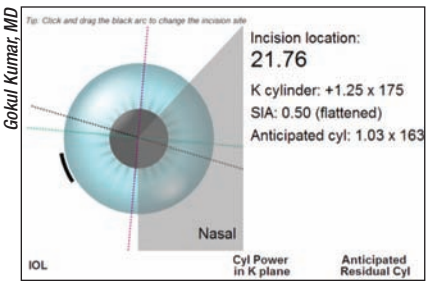
Exchanging data instantly via the Internet has revolutionized social networking and retail business, and it didn't take long for medicine to feel the effects. With the touch of a button, you can track your cataract outcomes, get a better understanding of the effects of your anti-VEGF injections and compare your glaucoma treatment results with ophthalmologists around the country. Here are three new Internet-server-based technologies—two of them free—that may be able to help you maximize your results.

Threeplus.org

The free website Threeplus.org was created by Aaron Lee, MD, and Gokul Kumar, MD, as they completed their ophthalmology residency at Washington University in St. Louis. The site offers several options for outcomes tracking and surgical planning.

"It's a combination of several things," explains Dr. Kumar, currently chief resident at Washington University. "First, we wanted to create a professional networking site just for professional ophthalmologists on both an invite- and inquiry-based log-in system. You create a free account and log in with your name. Second, we wanted a free way to properly track cataract outcomes.

"Initially the site allowed you to record what your surgery's target was, what lens you put in and then your actual result," Dr. Kumar continues. "However, we decided that we could do a lot with preop planning as well, using surgeons' outcome data to plan future surgeries. So, by using your actual postop outcomes data, the site calculates everything for your future cataract surgeries. Also, all this information is backed up on a server, so there's no worry over losing your data."



Gokul Kumar, MD

The free website Threeplus.org allows you to virtually rotate your incision location to different meridians until you find the one that results in the least induced cylinder.

One of the first things the surgeon can do on the site is track his surgically induced astigmatism. To do this, he inputs all the variables he'd need for SIA calculation, focusing on the astigmatism amount, preexisting keratometry and the location of the incision. Next, the physician can delve into the intraocular lens calculation formulas to help choose a lens.

"If you go to the New Preop section, used for planning the next case, you first determine an identifier you want to use for the case," explains Dr. Kumar. "Then you do the data input you'd need for the IOL calculation and determining SIA, which is basically the K readings, the axial length and the axis of astigmatism, all derived from whatever source you want. All the other data points you can enter are optional.

"Step three involves picking your blade," Dr. Kumar continues. "So, people can add custom blades and see what SIAs result from their use of them. We also have default values, such as -0.5 D SIA for a 2.75-mm blade, which is what the Alcon IOL Calculator uses. Or you can have your actual data calculated, and the site

The tear film is more than just a few drops of water.
It's a complex microenvironment.

THERA® TEARS

TheraTears® with Osmo-Correction™ Restores Eyes' Natural Balance™

Increased tear film osmolarity is one of the primary causes of dry eye symptoms.[1] TheraTears® with Osmo-Correction™ is a unique hypotonic and electrolyte balanced formula that replicates the natural human tear film and corrects osmolarity imbalance.

ADVANCED® VISION RESEARCH
AN AKORN COMPANY

1. DEWS Report, The Ocular Surface, April 2007; 5(2): 69-204

www.theratears.com

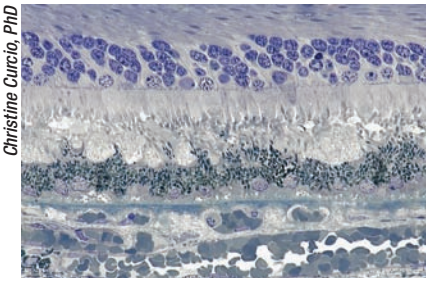
will allow you to pick your blade size, incorporating your own data, or you can enter a custom blade. In the next step you pick where to put the incision. On our site, you 'hold' the incision virtually on the screen and move it around the cornea. As you do this, the system tells you what your anticipated residual astigmatism would be. It also tells you what your anticipated residual cylinder would be for all the current toric lenses."

The next three steps involve lens calculations. "Pick whatever lens you want to go with, and on the back end we have all three major third-generation formulas—the Hoffer Q, Holladay I and SRK-T—and our site calculates your lenses and their anticipated residual sphere outcome," explains Dr. Kumar. "It does this for all the data that you've entered, so it shows you your personalized outcome estimates as well as what the ULIB [User Group for Laser Interference Biometry] estimates would be."

Membership on the site is by invitation, but surgeons can get an invitation by e-mailing support@threeplus.org and providing details about their ophthalmology training, contact information and current professional email address. Though the site will continuously add new lenses and other features to stay current, Dr. Kumar says it will remain easy on the wallet: "It's a free site and we intend on keeping it free," he says.

AAO's IRIS Registry

Capitalizing on a trend in other medical specialties in which physicians constantly update a registry with their latest outcomes from surgery and other interventions, the American Academy of Ophthalmology is rolling out a database of its own: the Intelligent Research In Sight Registry. William Rich III, MD, the Academy's medical director of health policy, says the system will, among other things, track outcomes with an eye toward improving them, provide opportunities for new research and help practices comply with new electronic reporting standards mandated by the government.



Christine Curcio, PhD

Project MACULA provides high-res histology images of multiple retinal layers. Here, histology revealed the presence of a subretinal drusenoid deposit.

The key element of the registry is a program called the Systems Integrator, created by software maker FigMD. "The Systems Integrator software sits on top of the practice's EHR program and draws out the data as it's entered," explains Dr. Rich. "For instance, it enters the outcomes from cataract patients and loads them into the registry without affecting the practice's workflow." If a practice doesn't have an EHR program, it can enter the data via an on-line portal, though Dr. Rich acknowledges this route would be more time-consuming.

Dr. Rich says the IRIS Registry will enable practices to do some things their EHR systems do not. "The EHR doesn't help you measure the quality of your outcomes," he says. "For example, the registry will take every user's input for a glaucoma patient or a cataract surgery case and, within 48 hours of completing the treatment, the physicians will be able to compare their results with anyone in their group, their region, or with a national database. That aggregated data is incredibly powerful."

Dr. Rich says tracking outcomes in a registry will allow physicians to gauge a therapy's effectiveness in the real world. "The problem is that randomized clinical trials are done on a very homogeneous subset of people, but once a treatment is approved by the FDA it's then used on people who are very different from those who were in the clinical trials," Dr. Rich says. "So, with a registry such as this, we will be able to find out which one of these drugs, devices or procedures is actually effective for large populations and for subgroups of populations." He adds that this type of tracking will be valuable as Medicare metrics change in the future. "Now, we get paid on how we treat the patient in front of us," he says. "But, starting in 2015, you'll get paid for how you treat the whole patient population. For instance, you can pull out all the diabetics under your care and see how they do, as well as how they compare to other diabetics in other practice populations in the United States."

IRIS also allows users to slice and dice their data in different ways to look for trends. "You can see how many glaucoma patients are on generic vs. non-generics and if there's a difference in safety or efficacy between generic and non-generic drugs," Dr. Rich explains.

"Floppy-iris syndrome, for instance, took us almost a decade to discover," Dr. Rich continues. "David Chang discovered he was having more complications, and had a fellow look at the records of the patients he had a complication with, and they found that these patients were 95 percent male. They then looked at their medication history and made the connection. With the IRIS Registry, you'd just have to push a button and ask: How many broken capsules are there, and is there any race, sex or use of meds in which this complication is greater? You could figure this out in a week rather than in 10 years."

The AAO plans to roll out the IRIS Registry officially at the 2013 national meeting. The cost to be enrolled will

TearScience®

The Evaporative Dry Eye Experts

Optimize Care, Enhance Your Practice

Improve Lipid Secretions, Increase Comfort, Satisfy Patients

LipiView® INTERFEROMETER

LipiFlow® THERMAL PULSATION

Alex Cohen, MD, PhD
Dean McGee Eye Institute
Oklahoma City, OK

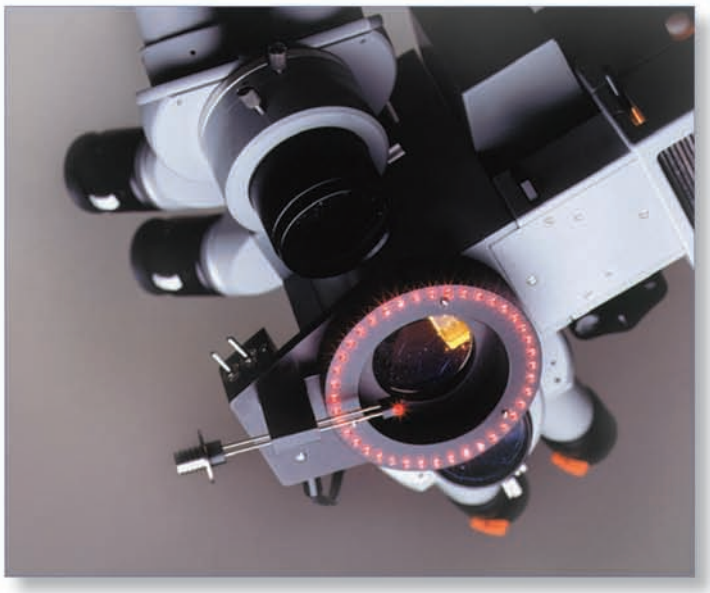
Recognize the Impact of Meibomian Gland Dysfunction, Seize the Opportunity

"TearScience® gives us another weapon in our arsenal to treat dry eye and stabilize the tear film. It has been gratifying to help patients frustrated with the results of traditional therapies."

LipiFlow® is clinically proven and the only currently available medical device indicated for Meibomian Gland Dysfunction (MGD).

Visit tearscience.com for complete product and safety information.

13-ADV-120 REV.A



360° FIXATION TARGET / OPERATIVE KERATOMETER

The simple inexpensive add-on to the operative microscope gives the surgeon instant qualitative operative keratometry at any time. It eliminates worry about ocular torsion when the patient lies down as it identifies positively the appropriate axis for astigmatic keratotomy. It eliminates the chilling possibility of a "90 degree error". Its movable fixation light can be rotated continuously over 360° to have the patient fixate on whatever position is best for the surgeon to make incisions. It is the ideal instrument to facilitate astigmatic keratotomy with cataract and refractive lens surgery.

CHAN WRISTREST

The Varitronics Chan Wristrest is the standard for stabilization of the surgeon's hands for ophthalmic surgery. Its height is easily adjustable and its bar can be rotated to adjust the distance to the patient's eye. It allows for the stabilization of the surgeon's arm and wrist to permit maximum control of the fine finger movements necessary for eye surgery. Its long aluminum base plate which is placed under the operating table pad makes it adaptable to any operating table. Like all Varitronics equipment, it is built to last indefinitely.

SURGICAL STOOL

The Varitronics hydraulic surgical stool is the ideal stool for the eye surgeon. It has a large comfortable seat, wide stable base, and foot bar/height control which allows the surgeon to change the height of the stool easily and gently by foot while operating.

NEVYAS DRAPE RETRACTOR

Increase patient comfort by keeping the drape away from the patient's nose and mouth. Reduce patient anxiety.

AUTOSWITCH CONTROL SYSTEMS

Varitronics Ophthalmic Control Systems will control your room and fixation lighting automatically and put your instruments at your fingertips. In-cabinet and desktop models available.

ETL Approved

EYEDENTIFIERS

Be certain which eye is to be operated.

VARITRONICS

See us at AAO Booth #3729

CALL TOLL FREE

800-345-1244

ph: 610.356.3995 / fax: 610.356.5222
e-mail: varimed@varitronics.com
www.varitronics.com

be $500 per year. However, Dr. Rich says that, during the initial roll-out phase, the first 2,000 practices that enroll can use the registry free for two years. To find out more about the early enrollment, e-mail irisregistry@aao.org. For more information about the registry, visit aao.org/iris-registry.

Project MACULA

For physicians who follow patients with age-related macular degeneration, especially those who use ocular coherence tomography, it can be challenging to match up the digital images to what's actually going on in the retina. To help make this interpretation easier, Christine Curcio, PhD, director of the AMD Histopathology Lab at the University of Alabama, Birmingham, helped create the free website Project MACULA, or MAClopathy Unveiled by Laminar Analysis.

Project MACULA is a website funded by the National Eye Institute that contains large, digitized sections of the macula taken from eye-bank specimens of wet and dry AMD, as well as from normal retinas. "It's effectively online digital microscope views," explains Dr. Curcio. "The idea here is to aid ophthalmologists and eye-care professionals in their interpretation of clinical imaging, such as OCT, by providing histopathology. The images are from specimens that I received from Alabama Eye Bank; they're short postmortem with a range of AMD pathology." The eyes, which will eventually number 140 and come with multiple images of different layers, also have 13,000 annotations that can inform doctors about certain features of the AMD pathology and show where the features are located in relation to the OCT image. Users can zoom in on the features up close using the patented GoogleMaps technology famous for detailed geographic mapping.

Dr. Curcio says the project even revealed features never before seen: "I went through each individual section of the specimens at defined locations," she says. "So they've been systematically, objectively surveyed. I crossed each layer with a vertical probe and noted what I saw. One of the big findings was subretinal drusenoid deposits. This feature had been seen clinically in patients but its histopathological correlate was uncertain before these images."

Dr. Curcio says that the website (http://projectmacula.cis.uab.edu/) should be done by late October 2013. "I hope clinicians find information on how to better interpret their diagnostic images from this site," she says. REVIEW

Dry-Eye Diagnosis: 21st-Century Tools

Christopher Kent, Senior Editor

As technology advances, our ability to uncover and monitor the disease continues to improve.

Dry eye is one of the most common problems encountered by ophthalmologists, but its multiple causes have made it a challenge to treat—and a challenge to diagnose. "Dry eye is a number of different conditions that I generally group together as ocular surface disease," says Christopher J. Rapuano, MD, professor of ophthalmology, director of the Cornea Service and co-director of the Refractive Surgery Department at the Wills Eye Institute in Philadelphia. "I think of dry eye as falling into two somewhat artificial categories: decreased tear production, or aqueous deficiency—which has classically been considered to be dry eye; and meibomian gland dysfunction, or evaporative dry eye. Unfortunately, there is no gold standard test, exam finding or even symptom for diagnosing dry eye. We have to rely on a constellation of signs and symptoms and test results to give us an idea of the patient's status."

Terrence P. O'Brien, MD, professor of ophthalmology, Charlotte Breyer Rodgers Distinguished Chair and director of the Refractive Surgery Service at Bascom Palmer Eye Institute of the Palm Beaches, agrees that there's no gold standard test for dry eye. "Over the years we've had to rely on the patient's history, plus symptoms and a composite of clinical tests to make a diagnosis—especially because the patient's symptoms often don't match the clinical signs," he says. "The Schirmer test has less than 50 percent sensitivity; tear-film breakup time is more sensitive but lacks specificity. Corneal staining is primarily only helpful late in the course of the disease; and questionnaires, although they've been validated, only have about 80 percent sensitivity and 72 percent specificity. Clinicians and patients are literally crying for better objective diagnostic tests for dry eye disease."

The need for better dry-eye diagnostic tools has spurred many researchers and companies into action, and the result is an increasing number of every-more-sophisticated instruments—some already available in the United States, and others still in the pipeline. Eight of the most promising are profiled below.

The First Wave: TearLab

One of the first high-tech diagnostic tools to appear was the TearLab Osmolarity Test. Although the test is widely used, there appear to be limits to how much can be determined by testing this one factor.

"Changes in osmolarity and

One Plug
One Size

SnugPlug™

That's *all* you need!

One-size-fits-all punctum plug
eliminates sizing and **simplifies stocking**

Pre-stretched shape (on inserter)
avoids dilation and **facilitates insertion**

Expanded shape (once inserted)
assures snug fit and **virtually eliminates pop-out**

Soft collar prevents migration
and **provides patient comfort**

Ophthalmics
FCI

FCI-Ophthalmics.com
800.932.4202

Plug into FCI for Dry Eye Treatment and watch the SnugPlug insertion video.

Visit PlugintoFCI.com for promotional pricing

inflammation are cited in the definition of dry eye from the 2007 Dry Eye Workshop report," notes Dr. O'Brien. "So measuring osmolarity should be helpful. The TearLab device, which does this reliably, is easy to use, and it's been shown to have analytical accuracy. However, in practice one of the challenges has been reproducibility and interpretation. Compensatory mechanisms often affect the eyes transiently and asymmetrically, giving rise to variability so that we have to test both eyes; and tear instability leads to evaporative tear loss, which can change the osmolarity. As a result, the TearLab osmometer gives you an accurate reading, but what the reading means at a given moment in the clinical course may be up for debate.

Terrence P. O'Brien, MD

The TearLab device allows the clinician to monitor the osmolarity of the tear film, a factor known to correlate with dry eye.

"The severity of the condition also matters," he continues. "Less severe eyes, which are often more challenging to diagnose, have considerable variability in osmolarity readings, so the test is less useful. The device seems to work pretty well for eyes that have more severe dryness; in those cases, it provides a baseline of severity and gives you a way to track the recovery or normalization of the osmolarity in response to therapy. However, those usually aren't the patients we debate about in terms of a diagnosis. So when diagnosing patients with less severe disease, we've found the TearLab platform to be most useful in combination with other tests, rather than by itself."

"There's no question that tear osmolarity goes up in dry eye, and there is a threshold," agrees Stephen C. Pflugfelder, MD, professor and director of the Ocular Surface Center at Baylor College of Medicine's Cullen Eye Institute in Houston. "The problem is that the TearLab instrument is fairly variable, so a single reading could be falsely low or high. The reliability improves with multiple readings, but that gets to be costly. In my opinion, a single measurement in the office is valuable primarily if it's abnormally high. If the test is normal but you think the patient has dry eye, you're probably going to go ahead and treat the patient regardless of the TearLab result."

Dr. Rapuano says his clinic has used the TearLab machine for about six months. "Osmolarity is a reasonable surrogate for dry eye," he notes. "We decided to try the TearLab because it was the most mature of the newer tests and seemed to have the most potential. Generally, the results confirm the impression we get from the slit-lamp exam. It is useful to have a somewhat objective number to look at; it gives us an idea of where patients are at this point in time."

Dr. Rapuano notes that a key part of getting an accurate TearLab measurement is taking the measurement before anything else has been done to the eye. "You can't put drops in, manipulate the eye or do an exam before using TearLab," he explains. "It has to be done first. That means you can't examine a patient and say, 'Oh, you have dry eye, now I'm going to do a TearLab on you.' In that situation, we usually tell the patient that we'll do the TearLab test the next time he comes in, before anyone has touched his eye. When new patients come in, we have a little dry-eye evaluation form we ask them to fill out, to hopefully alert us to the problem before anything else happens.

"I think the TearLab is a nice addition to our armamentarium," he concludes. "I don't think it's the end-all and be-all, but it's helpful, especially when it gives a result I'm not expecting. If I think the patient has really bad dry eye but the tear osmolarity is low, then I look back and consider other possibilities I might not have been thinking about. If the osmolarity reading is unexpectedly high, I know that dry eye may be more of an issue than I initially thought. That only happens on occasion, but that's when I find it most helpful."

The RPS InflammaDry

One of the newer dry eye diagnostic tools is the InflammaDry Detector from Rapid Pathogen Screening in Sarasota, Fla., which detects levels of matrix metalloprotease 9, or MMP-9, in a tear sample. MMP-9 is considered to be a reliable marker for the presence of inflammation, commonly associated with dry eye.

Dr. O'Brien says he's excited about the potential of using inflammation as a biomarker to aid in the diagnosis of dry eye. "A number of inflammatory markers have been identified in tears," he notes. "Lactoferrin, lysozyme, cytokines and other tear-film markers offer great potential, and having the ability to detect inflammation can be useful both for diagnosis and tracking response to therapy. So we're excited about having a device that can reliably and accurately detect levels of MMP-9 in the tear film.

"Increased MMP-9 can contribute to a number of problems, including disruption of the corneal epithelial barrier, decreased surface regularity

#EHRfail

Your EHR is in the Spotlight. Are you ready?

Industry insiders suggest 50% of all EHR systems will not make it through Meaningful Use Stages 2 and 3 Certification requirements.[1] Protect your practice from a major #EHRfail and choose an EHR system that WILL deliver. Healthcare is increasingly built around rules, regulations, code, and transparency. **Choose an EHR with proven stability and success.**

Medflow delivers what you need in an EHR provider.

- ☐ MU2 — Meaningful Use Stage 2
- ☐ ICD 10
- ☐ Health Information Exchange
- ☐ $? — RAC Audit Protection
- ☐ EHR Interoperability
- ☐ Staff Training
- ☐ Data Backup
- ☐ Mobile Access
- ☐ Cloud-Based Solutions
- ☐ Patient Portal
- ☐ Data Visualization
- ☐ [404] — Coding Error Prevention
- ☐ Automated PQRS Reporting
- ☐ Eye-Care Specific Workflow
- ☐ DICOM Compliant

Medflow

www.medflow.com | 855-MEDFLOW

Eyecare's leading EHR solution.

AAO 2013 Booth 3313

1 Black Book Rankings 2013 Survey of EHR consultants, analysts, managers and support team members: www.blackbookrankings.com/healthcare/

For more information, log onto one of our **Meaningful Use Stage 2 webinars.**

October 28 at 5:00PM Eastern
November 11 at 4:30PM Eastern
Register at **www.medflow.com**

Terrence P. O'Brien, MD

The RPS InflammaDry Detector detects levels of matrix metallo-protease 9, or MMP-9, in a tear sample. MMP-9 is considered to be a reliable marker for the presence of inflammation, commonly associated with dry eye.

and increased cell turnover," he explains. "It really is a marker for dry eye; studies have confirmed that patients who have ocular surface disease with dry eye have elevated levels of MMP-9 in the tears. In fact, I think it's a more sensitive diagnostic marker than clinical signs, and it correlates well with our exam findings. The sensitivity is 85 to 90 percent, with a specificity around 95 percent. That's quite beneficial.

"Our data suggests that people without dry eye or other ocular surface disease have between 3 and 40 µg/ml of MMP-9 in their tears; above 40 µg/ml is elevated and abnormal," he continues. "The readings correlate well with the different levels of dry-eye severity, based on the DEWS severity criteria. I think this is a good test, especially since it demonstrates a good correlation in milder cases, which can be problematic to detect with the osmolarity test."

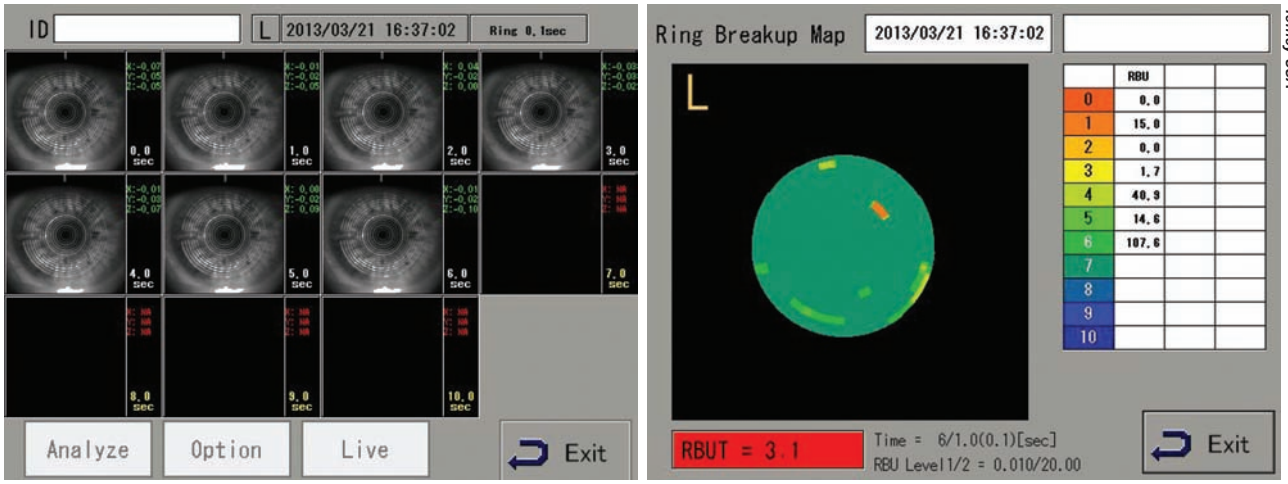
Is MMP-9 the best choice of marker to measure? "There are a variety of proteins altered in dry eye, but MMP-9 is one that's consistently been shown to be elevated with dry eye and normal in people without dry eye," Dr. O'Brien notes. "Clearly there are other conditions in which MMP-9 can be elevated, but those are obvious from the clinical presentation. Even though it's only one matrix metalloprotease, it's a common one that's been well-studied and shown to be abnormal in these patients."

Another advantage of measuring MMP-9 is that it appears to indicate a likelihood that certain treatments will be effective. "When MMP-9 is elevated above 40 µg/ml, patients will respond better to anti-inflammatory therapies, both corticosteroids and immunomodulatory agents like cyclosporine, tacrolimus and others," says Dr. O'Brien. "Knowing the osmolarity, in contrast, is less helpful in terms of directing your therapy or predicting patient response to specific treatments."

Monitoring Tear Film Instability

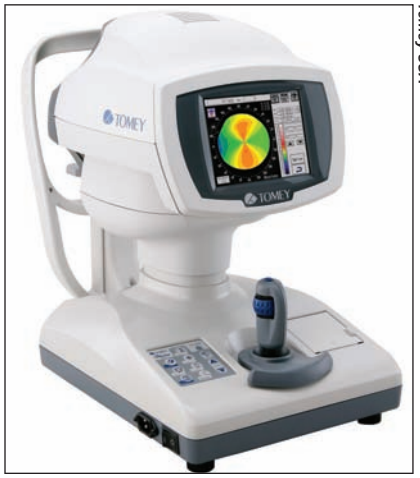
"One key to diagnosing tear dysfunction or dry eye is instability of the tear film," notes Dr. Pflugfelder. "Instability is pretty much found in all tear dysfunction problems—including meibomian gland dysfunction, conjunctivochalasis, aqueous tear dysfunction and Sjögren's syndrome—whether there's a low tear volume or not. One new device that can help measure that factor is the Tear Stability Analysis System, or TSAS, from Tomey.

"The TSAS device was developed in Japan," he continues. "As far as we know, we're the only center in the United States that has published a study using the device. It's very useful.



Tomey USA

Tomey's Tear Stability Analysis System reflects rings off the surface of the tear film while taking a series of pictures, one per second. The instrument then calculates the number of areas of irregularity appearing over time and displays the results graphically. Physicians report that a more rapid climb in the irregularity score correlates with the severity of dry eye.



Tomey USA

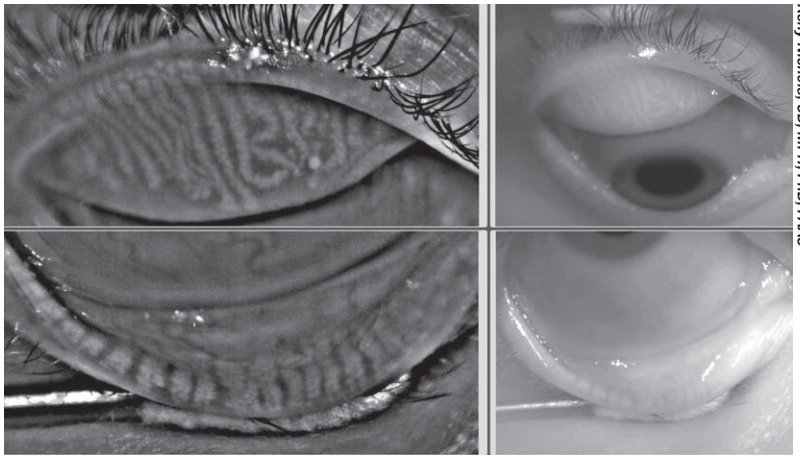
The Tear Stability Analysis System.

Over a period of six seconds, it takes a series of images of rings reflected off the tear film, one per second. The software then analyzes the images and calculates the number of what the company calls bright spots, which are areas of irregularity. The higher the number of bright spots, the more unstable or irregular the tear film is becoming. You can plot that out over the six seconds to show how rapidly the tear film becomes irregular.

"In the study we conducted, we used this technology with dry eye of different clinical severity levels, from one to four," he says. "We found a clear correlation: The more clinically severe the dry eye, the more rapidly the irregularity score went up. It provided valuable information, even early in the disease. It's a test I would use on every patient, except that we can't get reimbursed for it. Right now there's no billing code. It's approved, but not reimbursable."

Meibography Plus

Another factor potentially contributing to dry eye is the condition of the meibomian glands. Several new devices that have appeared in the recent past aim to make meibography quicker and easier. One that includes multiple dry-eye-related tests is the



Kelly Nichols, OD, MPH, PhD, FAAO

The Oculus Keratograph 5M (above) performs multiple tests relating to dry eye, including meibography (right). Automatic enhancement of the images allows easier visualization of the meibomian glands.

Keratograph 5M from Oculus.

"We bought the Oculus Keratograph 5 because of the meibography, but we use it in a couple of ways," explains Kelly Nichols, OD, MPH, PhD, FAAO— FERV Professor at the University of Houston College of Optometry and director of The Ocular Surface Institute at the university. "In terms of meibography, when taking images the instrument provides a little more guidance than previous models, such as showing you where to center the lid in the box. Once you've taken the picture, it automatically enhances the contrast of the image so you can get a clearer view of the glands. The company is also working on a grading algorithm for what's normal and abnormal; I'm hopeful that in the future we'll be able to compare a patient to an age-matched sample, or to previous images of the same patient.

"The Keratograph 5M also has tests that were not part of the previous model, as well as tests that have been enhanced, which the company refers to as the dry-eye suite," she continues. "That includes a tool for measuring tear meniscus height. Once you have a photograph of the eye, you use a little onscreen widget tool that looks like a Roman capital letter I. You put the top bar of the capital I at the top of the tear meniscus, and the bottom bar at the lid margin; the program then gives you an exact measurement. This provides a level of accuracy that you couldn't get looking through a slit lamp, even with a reticule. Also, because you're measuring an image, you don't have to worry about the patient moving. You can take measurements all the way across the lid margin, if desired.

"Actually, we use this more in clinical research than in clinical practice," she notes. "I believe that in practice a global assessment of whether the patient has tear prism or not is almost as good as having a quantified measure. But it might be valuable for comparing how contact lenses affect the tear film, or if the eyes have significant differences in epiphora."

Dr. Nichols says the Keratograph 5M also does a noninvasive tear breakup time test. "It gives you a color map showing what regions of the tear film are breaking up," she explains. "The map looks a lot like a topography map; color coding tells you how quickly the tear film broke up in each area. However, we've found this test takes some practice to run. To me it seems like it starts counting while the patient is still blinking, so it can be slightly off. New users might have trouble getting it to work, but with training staff can easily perform the test."

Dr. Nichols says the instrument also quantifies conjunctival redness. "To do this, you take a color photo," she says. "When you click the button, it creates a grayed-out circle in the center of your view which you overlay on top of the iris and pupil to mask them out of the picture. Then you press go, and the instrument gives you a measure of limbal and conjunctival redness. This is mostly helpful as an objective way to monitor improvement and show the patient that you're making progress but that's sometimes a valuable service."

Dr. Nichols notes two other, more qualitative measurements that can be made with the instrument's dry-eye suite at the push of a button. "The device allows you to view the lipid layer of the tear film, giving you an interferometry pattern," she says. "A lot of colored fringes indicate a thicker lipid layer. There's no measurement map associated with that, but if you use it a lot, I believe you could learn to gauge whether the lipid layer seems normal or not. This is similar to what the LipiView does, although the LipiView goes one step further; it measures the color of the output and gives you a number—an average lipid layer thickness.

"The device also allows you to see the speed at which the tear film moves upward after a blink," she adds. "You focus two white dots on the tear plane. As the patient blinks, you can see how fast the tear movement is occurring on the ocular surface, without any need to use a dye. A fast speed is normal;

The potential in the refractive market is growing.

How do you cultivate the opportunity for your practice?

When you provide patients with the opportunity to use financing options with the CareCredit® healthcare credit card, they can fit the refractive procedures they want into their monthly budget. Now, the potential for growth is expansive. Nearly 80 million members of Generation Y are moving into the ideal age for LASIK procedures*, while millions of Baby Boomers are becoming candidates for premium IOLs, lifestyle lenses, and more. CareCredit can help you plant the seeds to cultivate your share:

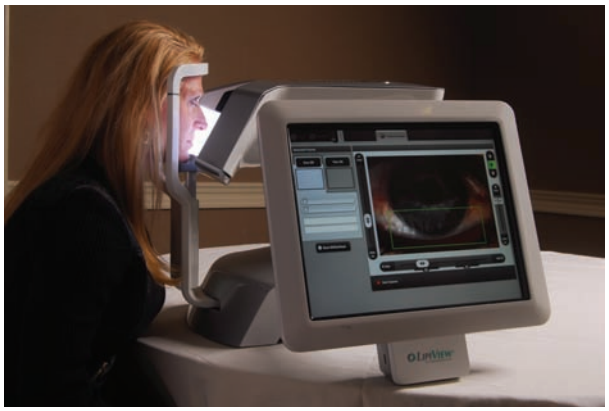
- A Practice Development Team dedicated to your success.
- A network of 7+ million cardholders approved for financing.
- A suite of FREE resources to maximize your practice's potential.

Millions of refractive opportunities are waiting.
Let's start cultivating your share now.

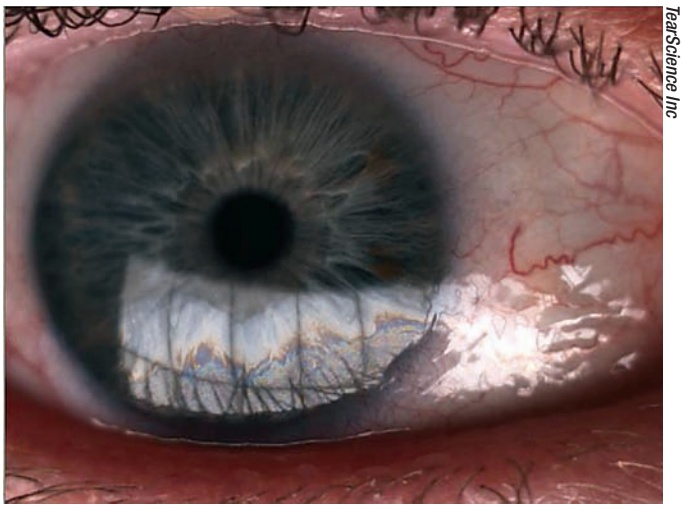
CareCredit℠
Making care possible...today.

CareCredit.com • 800.859.9975 option 1, then 6

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



The LipiView interferometer, part of the TearScience system that includes the LipiFlow treatment device, analyzes the thickness of the lipid layer of the tear film.



TearScience Inc

if it's very sluggish, or you see a lot of speckly stuff, that would be another indicator of an irregular tear film or lipid layer."

Dr. Nichols notes one other feature of the Keratograph that she appreciates: the camera. "For the money, it has a fantastic camera," she says. "It wouldn't be ideal for some purposes, such as taking pictures of corneal degenerations or small things on the cornea that require high magnification and a slit beam; but for a general photograph of the ocular surface—cornea, conjunctiva, lids, lashes, even fluorescein and tear breakup time, it provides a fantastic picture. Onscreen, you can digital zoom, fix the lighting, turn the gain up or down and make real-time adjustments. It takes better fluorescein photographs than any other method I've seen, without having to do any optimization. In contrast, most cameras attached to a slit lamp aren't optimized for viewing through a cobalt filter, for example.

"My opinion of all the extra tests in the Oculus dry-eye suite is that they do add some didactic value," she says. "Clinically, I don't know if I would use all of them; I probably would still do my regular tear breakup time test, and I'd look through the slit lamp at the elements of the tear film moving and tear meniscus height, etc. In any case, aside from the dry-eye tests and meibographer, this is a topographer first and foremost. But given all the functions it performs, I think you get a lot for your money. And like the LipiView, it's a step toward a functional, more objective way to evaluate the tear film and ocular surface in dry eye and other common diseases."

Dr. O'Brien's Ocular Surface Center clinic also has an Oculus Keratograph 5M. "This technology allows us to evaluate the condition of the meibomian glands; many people are now saying this may be useful in diagnosis," he says. "The preliminary results are encouraging, in terms of being able to detect MGD and tearfilm breakup time with more quantitative accuracy. The chief problem with diagnosing dry eye has been the semi-quantitative nature and variability with all of the tests, so the more quantifiable, reproducible and accurate the test, the better it will be. Oculus and several others are showing great promise as a means to provide that."

Another new meibography tool is a portable, handheld, pen-shaped device developed in Japan and manufactured by Topcon. The non-contact device incorporates an infrared LED light source and a sensitive video camera that can be connected to a monitor or computer; it provides a panoramic view of all of the meibomian glands along the upper or lower eyelid, without causing the patient any discomfort. The device is available for import but is currently not approved by the Food and Drug Administration. (For more on this, see "Breaking New Ground in Meibography" in the July 2013 issue of *Review*.)

Analyzing the Lipid Layer

Another tool that may be of use when diagnosing dry eye is the LipiView interferometer, part of the TearScience system that includes the LipiFlow treatment device. The LipiView is designed to analyze the thickness of the lipid layer of the tear film. Dr. Rapuano says his clinic uses the device. "We didn't buy it separately; it came with the LipiFlow device, and we use it because we have it," he explains. "Like the TearLab osmolarity test, the LipiView needs to be done before any drops are put in—certainly before you've examined the patient and pressed on the lids and gotten any lipids to come out. It's a completely noninvasive test; the patient sits and blinks at the screen. Since we like to use both tests, we do the LipiView first; the TearLab has a little collector that touches the eye, which could theoretically alter the LipiView results.

Trade Up To Keeler

Trade-in your old Kowa hand-held slit lamp & get $600 towards Keeler's Advanced PSL Classic!

Powerful & Portable!

- Precision machined aluminum chassis
- Advanced optics, x10 & x16 magnification
- Controllable illumination from maximum to zero
- Most Apertures and filters along with 1.mm square light patch for assessing a/c flare

Trade-in & Special Bonus
FREE iPhone 4 Adapter and Carrying Case.
Offer expires December 31, 2013.

Buy Online!
keelerusa.com

Keeler
OPTICS

Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008 • Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

"The LipiView test is designed to measure the thickness of the lipid layer, but we have not found that to be very helpful," he continues. "It doesn't seem to correlate too well with people's slit lamp exams or symptoms, or with what we think of as the severity of blepharitis. I'm not sure whether that's a technological issue, or if the thickness of the lipid layer really isn't a determinant of lipid layer function. It doesn't really help us determine whether the patient is a good candidate for LipiFlow; instead, I determine that based on the slit lamp exam and the symptoms. Nor does it correlate with whether the patient is successful with LipiFlow.

"The most interesting part of the LipiView test, in fact, is the little video of the patient blinking that you record as part of the test," he says. "The device gives you a printout that shows you who the partial blinkers are. This has nothing to do with the lipid layer thickness that the instrument is measuring, but for many patients, a partial blink is a big part of their problem. Unfortunately, there's no easy way to eliminate partial blinking, but at least we can tell the patient, 'This is why the 20 medications and treatments you've tried for this issue have not worked. You're not completely blinking, so the lower half of your cornea is getting dried out as the day goes on.' "

Dr. Nichols also has used the LipiView device. "In practice, we've found patients with seemingly normal lipid layer thickness on the LipiView test; but you look at their secretions and their meibography and they're not normal," she says. "Maybe they just rubbed the eye and expressed some lipid. There's a lot we don't know yet, but it's clear that you can't use any one of these tests alone."

Dr. O'Brien says the Ocular Surface Center clinic at Bascom Palmer Eye Institute has a LipiView device, but has only recently been gaining experience with screening dry-eye popu-

Advanced Tear Diagnostics

The TearScan MicroAssay System quantifies levels of lactoferrin (a dry-eye marker) and IgE (an allergy marker) in the tear film, helping to distinguish dry eye from allergy problems.

lations. "It produces very intriguing high-tech images, but the interpretation is still difficult," he says. "I'm not sure we fully understand yet exactly what the patterns mean or how they correlate to clinical disease. However, it's been useful for catching partial blinkers, and it's been useful as a patient education tool, letting us show patients why they're uncomfortable or having problems."

The TearScan MicroAssay

Another new tool designed to allow quantification of key markers in the tear film is the TearScan MicroAssay System from Advanced Tear Diagnostics; it measures markers relating to both dry eye and allergy. "There's a lot of art to treating dry eyes, and the science is lagging behind," notes Young Choi, MD, medical director of InVision Ophthalmology in Homewood, Ala., who has used the TearScan MicroAssay System for almost a year. "However, I think the diagnostic machines are starting to catch up. This instrument, for example, is able to quantify both lactoferrin and IgE in the tears. It's extremely sensitive and specific. It's reproducible and accurate, and we know that lactoferrin level is indicative of dry eye. So it tells you a lot about your patient's condition."

Dr. Choi says the fact that the MicroAssay System also measures an allergy-related marker (IgE) is very helpful. "One of the big advantages of this system is that the IgE reading tells me if the problem is more irritation from allergy than dryness," he says. "There's a lot of overlap between aqueous-deficiency dryness, evaporative dryness and allergy dryness.

"This kind of consistent, reproducible data will help tease out some of this overlap and help us fine-tune our treatment regimen," he notes. "We won't have to do a shotgun approach and put every patient on the same thing. Maybe we can say, 'Yours is really more of an aqueous production problem; let us help you make more tears.' Or, 'Yours has an allergy component to it, so we'll treat for both allergy and dry eye.' Now we're addressing more of the actual problem.

"Of course, this is all new; no one has been routinely measuring lactoferrin in the tear film," he says. "We don't fully understand what the role of lactoferrin is. For that reason we're gathering data to get a better idea of the clinical consequences of different lactoferrin levels. Does this indicate more aqueous deficiency dry eye, or evaporative dry eye?"

Dr Choi says he believes this information will become even more useful as time goes on, and may have a role beyond just diagnosing and treating dry eyes. "For example, this could be an important tool for screening LASIK patients, because lactoferrin may make a difference in outcomes," he says. "An ARVO poster a few years ago reported an association between lactoferrin level and whether LASIK eyes came out over- or undercorrected. Since it gives us a precise number, we may be able to associate specific levels of lactoferrin with specific amounts of over- or undercorrection."

Dr. Choi says he believes the TearScan MicroAssay System is ready for prime time. "It's only a few thousand dollars, which is a fraction of

the cost of some other machines out there," he observes. "The data is consistent and reproducible, and there's evidence that lactoferrin levels are associated with dry eyes. You have something you can hang your hat on. I see this as a big step forward in terms of putting more science into diagnosing and treating dry eyes."

Diagnosing Dry Eye with OCT

"Several of the currently available optical coherence tomography devices can help the clinician determine whether the tear volume is reduced, by noninvasively measuring tear meniscus dimensions," says Dr. Pflugfelder. "That tells us whether the patient has an aqueous deficiency or not, which can point the diagnosis in a different direction. We use the Optovue OCT for this; Zeiss makes the Cirrus OCT, and there may be other OCTs with this capability. In fact, our Optovue has software specifically designed to measure the tear meniscus dimensions.

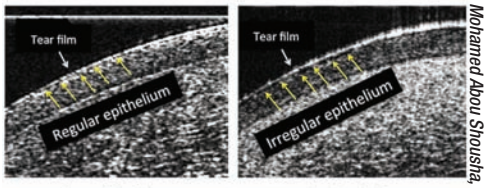
"We find this feature extremely helpful, and we now use it on every patient," he continues. "We can measure the height, width or area of the lower meniscus, which has been found to be a good measure of total tear volume. It just takes a few seconds to image that, and it gives you a good sense of how much aqueous fluid is on the eye. It can replace more inaccurate tests like the Schirmer test. Unfortunately, OCT is not approved for imaging the tear film yet, so we can't bill for this test as a dry-eye diagnostic."

A number of Dr. O'Brien's colleagues at Bascom Palmer have been working on the possibility of diagnosing dry eye using real-time high-resolution OCT. "Our group has developed a prototype custom-built ultra-high-resolution spectral domain OCT device, or UHR-OCT, to study the ocular surface of dry-eye patients in a noninvasive fashion down to

resolutions of 2 to 3 µm," explains Victor L. Perez, MD, associate professor of ophthalmology, microbiology and immunology at the Bascom Palmer Eye Institute. "Utilizing UHR-OCT we've microscopically mapped the ocular surface; we've found that dry-eye patients have specific surface irregularities on their corneal epitheliums that can be measured and quantified using a diagnostic index that we've named epithelial irregularity factor, or EIF. *(See example, right.)* Those epithelial irregularities are most likely the microscopic structural injurious effects that dry-eye syndrome imposes on the ocular surface. Those microscopic structural changes seem to be readily detected by the unprecedented high resolving power of recently developed imaging devices such as our UHR-OCT.

"Our preliminary data has demonstrated that our novel dry-eye diagnostic index, the EIF, provides a noninvasive qualitative and quantitative means to diagnose dry-eye syndrome that correlates accurately with patients' signs and symptoms," he continues. "Moreover, our preliminary data have shown that EIF could be a tool for objectively and subjectively monitoring dry-eye response to treatment, and could be used to develop and test new therapies."

"These results are really exciting," he adds. "They show that EIF could address many of the limitations of the currently available diagnostic techniques. Spectral domain OCTs with such high resolution have already moved from research laboratories to clinics, and commercial models will soon become available to help improve the standard of care of our patients."



Mohamed Abou Shousha, MD

Optical coherence tomography can be used to assist in dry eye diagnosis. Some current in-office devices can be used to measure tear meniscus dimensions; newer, ultra-high resolution OCT is able to create a map of epithelial irregularity (example above) and quantify it. Researchers have found that this can not only differentiate healthy eyes from dry eyes, it can accurately indicate the severity of the dryness, useful for both diagnosis and monitoring during treatment.

Harvesting Cells for Testing

Although removing cells from the surface of the eye and sending them to a laboratory for testing is a more complex approach than some of the new point-of-service tests, it offers the advantage of allowing a far more detailed analysis—and the testing of the cells may soon become an in-office capability. Ironically, one reason this has been little used in the clinic is the difficulty of sampling cells from the ocular surface. Some companies are trying to address that.

"The EyePrim is a sampling device that's used to procure cells from the ocular surface for biological testing," explains Pierre Roy, CEO of OPIA Technologies in Paris, France. "It's reliable, fast, efficient and painless for the patient, without the need to use any anesthetic. The old technique, conjunctival impression, required anesthetic and was not reliable in 20 to 40 percent of cases; you often did not end up with enough biological material to conduct the test. In addition, it was more time-consuming and cumbersome and a bit painful for the patient. That's what inspired us to create the EyePrim device." (Mr. Roy notes that the idea originated with Christopher Baudouin, MD, professor and chair of ophthalmology at Quinze-Vingts Hospital in Paris.)

Currently, the device simply harvests cells from the conjunctival surface, but the company is working to develop it into a point-of-service test for dry-eye markers. "For example, you might sample the cells and discover that the ocular surface is missing mucous cells," he says. "That could explain the dry eye. And of course, we could also test for inflammatory biomarkers that are exploited by the cells when dry eye is present. Polymerase chain reaction testing is another possibility we're exploring.

"The device is simple to use," he continues. "You open the sterile, single-use pack and ask the patient to look down or up, depending on the area being sampled. You place the tip against the conjunctiva and gently press the plunger for a couple of seconds. Then you remove the device from the surface of the eye and eject the sample into the container that will be used for shipping to the laboratory.

OPIA Technologies

The EyePrim device allows quick, painless and reliable sampling of conjunctival cells, which can then be analyzed for markers of dry eye or other disease.

"The conjunctiva is a mucous tissue that is constantly renewing itself, like skin," he notes. "The EyePrim samples the most superficial layer of cells, cells that are about to be ejected into the tear film. The cells simply adhere to the surface; there's no scraping involved. The device is very safe, and the patient doesn't feel anything. There's no visible change on the surface of the eye, and the sampled

area heals within a matter of hours."

To test the efficacy of the device Mr. Roy says the company has conducted several clinical studies, one of which was done with a team from Birmingham, England. "They found that this procedure is about two times faster than the old procedure," he says. "It's also more efficient; they retrieved enough material for testing in 100 percent of the cases. On average, the device collected two to five times more cells than the older procedure, without the pain. That's especially important in a clinical trial, because if you sample patients three times over the course of the trial and 20 percent of your sampling fails to produce sufficient material for testing, you could have a 50-percent data loss. The ease of use was also clear; nurses are now using the device to take the samples instead of the doctors."

The EyePrim is currently being used in several clinical trials to measure biomarkers and evaluate the efficacy of the different treatments that are progressing toward marketing. The device, approved but not yet reimbursable, is distributed in the United States by Ocular Surface Diagnosis Innovation in Tampa. OSDI also offers biomarker-based diagnostic services, so samples can be shipped to them for testing.

Dr. Pflugfelder has used the EyePrim. "This kind of test would be very useful for diagnosing dry eye," he continues. "It's well-known that patients with aqueous tear deficiency show a decrease, and sometimes an absence, of goblet cells. Furthermore, the severity of irritation, light sensitivity and corneal/epithelial disease has been found to correlate with the number of goblet cells. So this would be an important parameter to measure. Also, Restasis increases the number of goblet cells; that may be one of its major mechanisms of action. So this might be a way to identify patients who would be good candidates for that treatment. In any case, the EyePrim is a great device." REVIEW

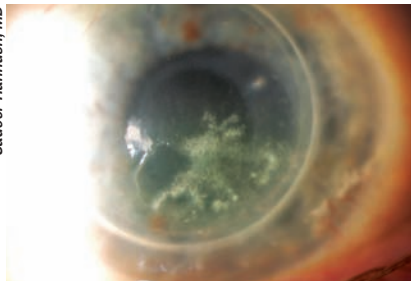
Dr. O'Brien has been a non-salaried ad hoc consultant/advisor for Rapid Pathogen Screening, TearLab, Advanced Tear Diagnostics and Tear Science. Dr. Choi is a consultant for Advanced Tear Diagnostics. Drs. Shousha and Perez have submitted a United States Provisional Patent Application for the HR-OCT technology. Dr. Nichols has no financial interest in Oculus or TearScience or their instruments. Drs. Pflugfelder and Rapuano have no financial ties to any company or product mentioned.

Meeting the Challenge Of Fungal Keratitis

Walter Bethke, Managing Editor

Cornea experts provide tips and techniques for dealing with these difficult infections.

To hear physicians tell it, battling fungal keratitis is like wrestling a bear with one hand tied behind your back: Fungal infections are notoriously resistant to treatment, penetrate deep into the cornea, take days to culture and weeks to heal, and there is only one commercially available antifungal agent—with the rest requiring a compounding pharmacy to produce. However, despite these obstacles, prompt diagnosis and quick treatment can yield a good outcome. In this article, corneal experts review how to diagnose fungal infections early and treat them properly.



Sadeer Hannush, MD

A history of corneal transplant, as in this case, is a risk factor for fungal infection.

Clinching the Diagnosis

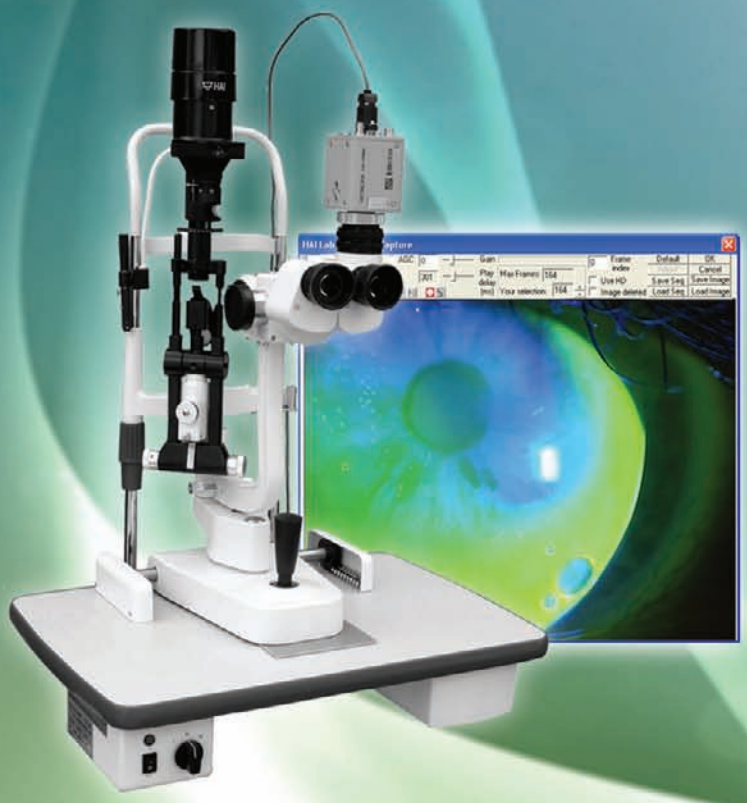
Physicians say that you increase your chances of saving the cornea by catching the fungus early and hitting it hard with medications. Here are their tips:

• ***Watch for the risk factors.*** "A major risk factor is where the clinician practices and where the patient lives or has visited recently," says Francis Mah, MD, a corneal specialist at the Scripps Clinic in La Jolla, Calif. "Fungal infections, and fungal keratitis specifically, are a lot more common in hot, humid areas. If an ulcer patient says he has recently traveled to Singapore, for example, that should raise your suspicion of a fungal cause since that could be the region where it started. The second factor to be aware of is the history. Specifically, agricultural causes, or causes involving trauma from a plant, will be a common factor. Also, contact lens use or misuse can be a frequent factor."

A fungus can also thrive in the setting of reduced immunity. "A risk factor can be immunocompromise, either biologically through cancer, HIV/AIDS or diabetes, or from medications," says Sadeer Hannush, MD, attending surgeon on the Cornea Service at Wills Eye Institute. "Medication causes can occur in transplant patients on immunomodulation in the eye or on systemic immunomodulation with an agent such as tacrolimus."

An unstable ocular surface can also pave the way for a fungal infection. "The other clinical setting to be wary of involves corneas in which ocular

HAI
Laboratories, Inc.

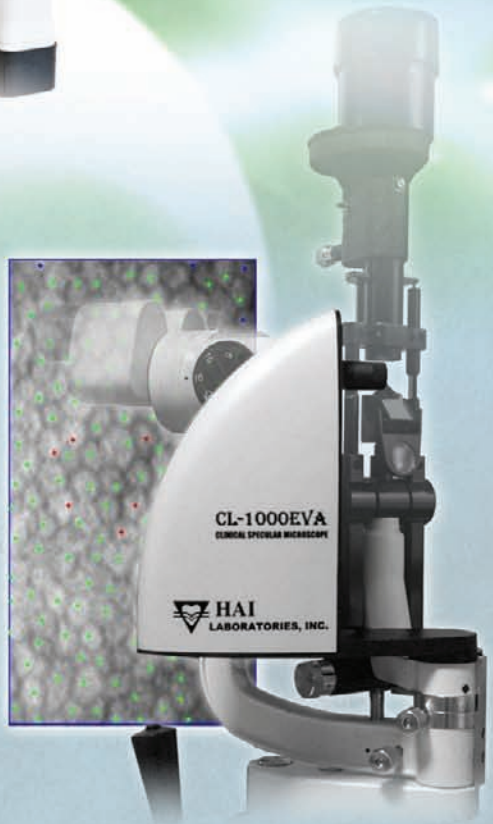


- American quality engineering
- Manufacturer-direct pricing
- On-site installation & training
- Purchase, rent or rent-to-own

LIVE DEMO
AAO NEW ORLEANS
BOOTH #2109

Bring new diagnostic power to your exam lanes, now with rent and rent-to-own flexible financing options.

Open up a world of possibilites with the HAI SL-5000 Digital Video Slit Lamp, the only anterior segment camera system that allows you to stream real-time high resolution video of the eye to an LCD monitor, big screen, projector, or over a network†. Capture clips or still photos with ease for education and documentation. With the addition of a HAI CL-1000eva Endothelium Viewing Attachment for slit lamps, get all the diagnostic power of a specular microscope in the smallest form factor (and price tag) available anywhere. On the go? The lightweight and ergonomic SL-5000h Handheld Slit Lamp with built-in 10x and 16x magnification is the perfect solution for your mobile needs.



Hightech American Industrial Laboratories, Inc.
320 Massachusetts Ave, Lexington, MA 02420, USA
Tel: (781) 862-9884 **Web:** www.hailabs.com

† Network streaming capability available with HAI IMS/CL Server Suite. Additional hardware required.

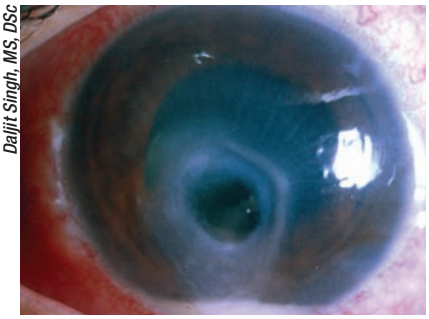
disease is chronic, with altered sensation contributing to an unhealthy ocular surface that can promote infection by a yeast, notably *Candida*, or other fungi," avers Terrence O'Brien, MD, professor of ophthalmology at the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine. "We've also observed fungal keratitis after LASIK with creation of a flap and associated dennervation, as well as after corneal transplant in which the patient's corneal nerves are compromised, there is foreign material present in the form of sutures and there's a concomitant use of a topical corticosteroid."

• ***Fungal features.*** Physicians say there are some features of fungal infections that stand out. "With bacteria, and even with *Acanthamoeba*, it's a really acute process," says Dr. Mah. "The eye will be normal one day and then painful with significant inflammation the next. Fungi take time to grow, so if the patient says his condition has been building for weeks, that may raise your suspicion of fungus.

"With fungus, you'll see satellite lesions," Dr. Mah continues. "These are pinpoint areas of infection across the cornea. Then, the infection will reach out and tend to go deeper than bacteria usually go." Physicians also say to be watchful for ulcers with feathery borders and which involve endothelial defects that come and go. In some cases, they say, the epithelium will actually be intact while the fungal ulcer grows beneath it. "Also," says Dr. Hannush, "in fungal keratitis the eye is often much quieter than you'd expect with a bacterial infection. So if I see a dense infiltrate, feathery or not, with an intact epithelium—or even without an intact epithelium—with a relatively quiet eye, I think atypical keratitis first, i.e., non-bacterial, specifically fungus."

Cultures, Stains and Tests

Corneal specialists say that, to make a definitive diagnosis before initiating treatment, tests are mandatory.



Daljit Singh, MS, DSc

Since fungal infections tend to grow deep, corneal perforation is a constant threat.

• ***Stains.*** For a possible quick confirmation, stains are an option. "Gram stain, specifically KOH stain, is what I do specifically for fungus, especially when I'm not certain what the microbe is," says Colleen Halfpenny, MD, assistant professor of ophthalmology at Jefferson Medical College in Philadelphia. Dr. O'Brien adds that other diagnostic stains can be employed, as well. "Giemsa staining can be helpful to identify the hyphal fungal fragments," he says. "Also, Gomori methenamine silver is a stain that aids visualization of the hyphal fragments, and calcofluor white can also be used to highlight the fungal cell wall."

• ***Cultures.*** It is usually easy to get a specimen for culturing when the pathogen is a fungus, physicians say. "If the epithelium is intact, you will have to debride it first," says Dr. Hannush. "And, you will have to scrape pretty aggressively. When you get a sample, the ideal culture medium is Sabouraud agar, but fungus will frequently grow on thioacrylate broth or blood agar." Sabouraud agar is preferred because it contains an antibacterial agent, and thus promotes fungal growth.

There may also be instances of polymicrobial infection. "In such cases you need to plate material on multiple selective culture media, such as blood agar, chocolate agar, Sabouraud agar, brain-heart infusion/gentamicin and thiol broth," says Dr. O'Brien.

Dr. Mah says the way you culture can affect the results. "You never want to culture the very center of an ulcer," he says. "This is because usually all that's left in the center is necrotic tissue and you don't actually get that much of the organism. Instead, you want to culture the edges of the ulcer. Grab a little of the viable epithelium if you can and put that on the culture plate. Also, you don't want to go to the base of the ulcer because if some melting has occurred you may cause a corneal perforation."

In cases where the epithelium is intact, some clinicians say you can still obtain material for culture without debriding the top layer of the cornea. "If the surface is uninvolved but there are branching filamentous infiltrates deep into the cornea, one method involving passage of a sterile suture can be helpful," says Dr. O'Brien. "One can pass an 8-0 silk suture through the cornea at the level of the suspected infiltrate. You can then carefully remove the suture, which has passed through the zone of suspicion and, using sterile scissors, cut pieces of it off to place directly on the culture media for submission to the microbiology laboratory."

• ***Biopsy.*** In some cases, corneal specialists say, the microbiological cultures will be inconclusive, and a biopsy can help make the diagnosis. Dr. O'Brien explains methods for performing a manual biopsy. "One can employ a single-use, sterile, dermatological skin punch of a specified diameter," he says. "The punch is used to obtain material from the cornea and then submit it for microbiology, histopathology or even molecular microbiology with PCR testing. Other times, you can use a 0.12 forceps to grasp the edge of the infiltrate and then use a #11 Bard-Parker sterile, single-use blade to perform a shaving biopsy."

Dr. O'Brien adds that, more recently, a femtosecond laser can be used to precisely, less-invasively and safely sample a specified area of the cornea for biopsy.

"Life-Changing"

"Dramatically Helped"

"Symptoms Gone"

Just some of the testimonials for Retaine® MGD™

Retaine® MGD™ Ophthalmic Emulsion is the only preservative-free artificial tear that utilizes electrostatic attraction to prolong corneal contact time and provide long-lasting relief of Dry Eye.

Retaine® MGD™ is like no other artificial tear and is sold through Eye Care Professionals only.

Do more...for your patients, for your practice.

Look for NEW Retaine® FLAX™ and Retaine® OM3™ Nutritional Supplements with Omega-3 and Omega-6 as well as additional Retaine® Brand Products coming soon!

To take advantage of this practice building opportunity, call (800) 233-5469 or visit Booth #4139 at AAO!

OCuSOFT®

Treatment

The agent or agents used to eliminate the fungal ulcer depend on the variety of fungus you're dealing with, experts say. The only commercially available agent is natamycin (Natacyn, Alcon), while the rest must be compounded. Here are tips for treatment.

• ***Medical therapy.*** "For an infection that's non-filamentous or mostly yeast, which is most commonly *Candida*, my treatment of choice would be topical amphotericin 0.15%, which most compounding pharmacies can prepare," says Dr. Halfpenny. "Topical capsofungin 0.5% can also be prepared at certain compounding pharmacies if there is too much toxicity from the amphotericin. Capsofungin is more expensive and harder to get, however."

Physicians say that, for filamentous fungi, they used to reach for voriconazole first, but all that has changed as a result of the recent multicenter Mycotic Ulcer Treatment Trial. In the trial, natamycin outperformed voriconazole, with natamycin patients being less likely to suffer a perforation or need therapeutic penetrating keratoplasty.[1]

"For filamentous fungus, my treatment of choice would be topical natamycin 5% or topical voriconazole 1%," says Dr. Halfpenny. "However, since the MUTT results were published, I tend to start with topical natamycin. For both filamentous and non-filamentous, I typically prescribe the drops to be used hourly around the clock for the first week, and then every two hours after that, depending on the patient's response. It often may take several weeks to see clinical improvement, so I'm not quick to taper unless there is significant toxicity from the drops."

One issue with treatment of fungal ulcers is the epithelium, since it can be intact in may cases. "Neither natamycin nor amphotericin penetrates the cornea well," says Dr. Halfpenny. "So, if the epithelium is pretty well healed when you see the patient but he has grown out fungus, I'll typically scrape the overlying epithelium before treatment. If he has an epithelial defect, though, I won't scrape."

The other treatment challenge is that fungal ulcers are often deep, and may need a two-pronged approach to treatment. "I will commonly start all patients with deeper ulcers on 400 mg oral voriconazole b.i.d.," says Dr. Halfpenny. "However, they need to have liver function tests at baseline and be monitored again every two weeks."

Finally, for very deep ulcers, some physicians use an intrastromal antifungal injection. "If the infection is very deep and you don't think you're getting good topical penetration, you can give intrastromal voriconazole," says Dr. Halfpenny. "This has been shown to be safe, but not much more effective than topical voriconazole in very small studies." Corneal experts say that, in general, they avoid the use of steroids in fungal ulcer management, as they've been shown to inhibit the effectiveness of antifungal therapy.

Clinicians say following the patient on therapy is as intense as the therapy itself. "One of the dictums with therapy is that it may get worse before it actually gets better," says Dr. O'Brien. "This is because as treatment begins to kill the fungi, there's a greater inflammatory reaction in the cornea. This is actually a sign of some improvement—it's just more inflamed but you're not seeing spread of the fungus. Positive signs of clinical response are a consolidation of the infiltrate, no sign of contiguous spread and the control of the satellite lesions."

Clinicians say they'll follow the patients daily or every other day while they're on hourly treatment, spreading out the visits to weekly or every other week if the ulcer responds to treatment and begins to consolidate. The treatment could last for months.

• ***Therapeutic graft.*** Despite the ophthalmologist's best efforts, medical treatment fails in 15 to 36 percent of cases.[2,3] When this occurs, a therapeutic keratoplasty is necessary. For the corneal specialist undertaking one of these grafts, here are the experts' tips.

When approaching the graft, Dr. Halfpenny has several considerations that she keeps in mind. "Try to keep the graft as small as possible, because it's likely that you'll need a secondary optical graft later, and you don't want that area to become vascularized and not allow the secondary graft," she says. "You should provide at least a 1- to 1.5-mm clear margin with the trephination, and be prepared to decenter the graft, if necessary. Also, you want to leave the patient phakic, even if he has the beginnings of a cataract, in order to leave a barrier to further fungal penetration or endophthalmitis. Postop, continue the oral or topical antifungal therapy and avoid topical or oral steroids for at least two to three days. You also should aggressively manage intraocular pressure with medications in the postop period because fungi have been known to destroy trabecular meshwork tissue. In light of this, the patient may need to see a glaucoma specialist or even require a secondary glaucoma surgery postop."

With the daunting course an ocular fungal infection poses as a global threat to corneal health, Dr. O'Brien hopes significant advances in the field will be made soon. "We're in desperate need of better antifungal agents that work more rapidly, penetrate more efficiently into ocular tissues and have fewer medical failures," he says. "We have to both discover and develop newer compounds with novel mechanisms of action, greater antifungal activity and less cytotoxicity." REVIEW

1. Prajna NV, Krishnan T, Mascarenhas J, et al. The mycotic ulcer treatment trial: A randomized trial comparing natamycin vs. voriconazole. JAMA Ophthalmol 2013;131:4:422-29.
2. Anane S, Ben Ayed N, Malek I, et al. Keratomycosis in the area of Tunis: Epidemiological data, diagnostic and therapeutic modalities [article in French]. Ann Biol Clin (Paris) 2010;68:4:441-47.
3. Prajna NV, Mascarenhas J, Krishnan T, et al. Comparison of natamycin and voriconazole for the treatment of fungal keratitis. Arch Ophthalmol 2010;128:6:672-78.

800.787.5426
haag-streit-usa.com

The source of more twinkling eyes.
The Haag-Streit LED.

Need to amp up the twinkle in your eye? Enter the Haag-Streit LED slit lamp powered by blue-shift illumination. It visualizes your subject in stunning detail with our celebrated optics.

But don't just take our word for it. See for yourself. Call 800.787.5426 for more information, or visit haag-streit-usa.com

The Superior Practice.

HAAG-STREIT USA

Can Treating Dry Eye Boost Your Bottom Line?

Michelle Stephenson, Contributing Editor

New technologies and the proper approach may tip the balance between the extra chair time required and extra profits.

In an effort to boost their practice's bottom line, some surgeons are finding success by expanding the diagnosis and treatment options to their dry-eye patient population.

One benefit of offering dry-eye services is that it can convert nonsurgical candidates to surgical candidates. "In a refractive surgery practice, there are patients who may not qualify for laser correction because of their meibomian gland dysfunction and dry eyes," says Sheldon Herzig, MD, medical director and co-founder of the Herzig Eye Institute in Toronto, Ontario, Canada. "Having an established dry-eye clinic to help these patients preoperatively, providing the most advanced technologies to perhaps restore normal tear function, can convert a non-candidate to one who does very well with refractive surgery."

Dr. Herzig notes that dry-eye patients can consume a lot of chair time in a busy practice, so having a dedicated dry-eye clinic that is appropriately staffed and equipped will not only deal with dry-eye disease more efficiently but will also help keep the practice running more efficiently.

Marguerite McDonald, MD, from Ophthalmic Consultants of Long Island in New York, has incorporated a dry-eye center of excellence in her practice. "There is signage about it everywhere, and there are booklets

Table 1. Example of Dry-Eye Patient's Visits/Charges
Chief Complaint: Blurry Vision

Description	Estimated Revenue(1)
New Patient, Comprehensive Exam (92004)	$144
One Month Follow-up Exam (99213)	$70
Three Month Follow-up Exam (99213)	$70
Twelve Month Follow-up Exam (99213)	$70
Total Annual Revenue Per Patient	**$354**
Other Potential Dry-Eye Treatment Revenue:	
Punctal Plugs (2) (1st eye $146, 2nd eye $73)	$219
Four Plugs	$370

(1) Assumes 2012 National Medicare Rates

Data in tables courtesy of Bruce Maller, BSM Consulting.

References
1. Christensen MT, Blackie CA, Korb DR, et al. An evaluation of the performance of a novel lubricant eye drop. Poster D692 presented at: The Association for Research in Vision and Ophthalmology Annual Meeting; May 2-6, 2010; Fort Lauderdale, FL. **2.** Davitt WF, Bloomenstein M, Christensen M, et al. Efficacy in patients with dry eye after treatment with a new lubricant eye drop formulation. *J Ocul Pharmacol Ther.* 2010;26(4):347-353. **3.** Data on file, Alcon. **4.** Wojtowica JC., et al. Pilot, Prospective, Randomized, Double-masked, Placebo-controlled Clinical Trial of an Omega-3 Supplement for Dry Eye. *Cornea* 2011:30(3) 308-314. **5.** Geerling G., et al. The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Management and Treatment of Meibomian Gland Dysfunction. IOVS 2011:52(4).

Systane®
Family of Products

Surface Protection and More

Alcon®
a Novartis company

and leaflets in every single room," she says. "We try hard to stay on time, but most patients have time to scan at least one brochure while they are waiting for the doctor to come in. Even if they haven't heard of us being a dry-eye center of excellence, they will leave knowing that we are, and they often tell their friends. There is a lot of word-of-mouth referral in a dry-eye practice. If you make an unhappy middle-aged dry-eye patient happy after she has been to five or six doctors, the halo effect is incredible. You are much more likely to get her daughter's LASIK and her father's cataract surgery."

All patients seen in the practice take a very short questionnaire. It takes them less than 30 seconds to check off whether or not they have symptoms of dry eye and the frequency of those symptoms. Tear osmolarity testing is ordered on any patient who checks off ocular surface symptoms on the questionnaire and on most patients who are 40 or older, because the incidence of dry-eye spikes in this age group. "Additionally, I order tear osmolarity on anyone presenting for any kind of ophthalmic surgery and on anyone with a history of dry eyes. Honestly, there aren't very many people in a cornea specialist's practice who don't get a tear osmolarity test as part of their exam," she says.

Dr. McDonald uses the results of the tear osmolarity test to guide therapy. A normal score is 290 to 295 mOsm/L. At this score, the tears are in homeostasis with the blood, which is normal and healthy. For every point above this score, the eyes are drier. If a patient is between 295 and 310 mOsm/L, she is asked to use artificial tears four times a day. In severe cases, patients are on lid scrubs twice a day and erythromycin ointment at night, low-dose doxycycline by mouth, artificial tears four to eight times a day, and nutritional supplements. This can be overwhelming for many patients. In these cases or in cases where the patient is unable to complete this regimen, Dr. McDonald offers LipiFlow.

Table 2. Revenue and Net Income Opportunity Dry-Eye Patient Population

	Dry Eye	Cataract Patients from Dry Eye	Glaucoma Patients from Dry Eye	Plug Patients from Dry Eye	Total Value from Dry Eye
Number of Patients	1,500	105 7%(1)	23 1.5%(2)	150	$743,350
Revenue Rate Per Patient(3)	$354	$1,600	$500	$219	
Gross Revenue	$531,000	$168,000	$11,500	$32,850	

(1) Assumes 50 percent capture of cataract prevalence from 2005 Gallup Study
(2) Assumes 50 percent capture of glaucoma prevalence from 2005 Gallup Study
(3) Revenue rates per patient are determined as follows:
- Dry Eye assumes $354 per patient per year with various office procedures
- (92004 = $144, three exams – 99213 = @ $70 each).
- Cataract assumes bilateral cataract surgery. Revenue rate includes surgery, exam and diagnostic testing.
- Glaucoma assumes revenue rate per patient with POAG and no systemic disease.
- Plug assumes first eye = $146, second eye = $73.

LipiFlow, LipiView and IPL

Adding LipiView, LipiFlow and intense pulsed light therapy to a practice is one way to boost revenue. "Dry eye is becoming a more attractive market now because there are more objective diagnostic tools and in-office therapeutic treatments that have expanded our armamentarium," says Elizabeth Yeu, MD, an assistant professor at Eastern Virginia Medical School and corneal specialist at Virginia Eye Consultants in Norfolk, VA.

LipiView is a diagnostic tool that, to a certain degree, quantifies the meibum and helps objectively gauge how patients may respond to a LipiFlow treatment, she adds. "LipiView provides a numerical measurement of the thickness of the lipid layer within the tear film, with value ranges that correlate this to posterior lid margin disease severity," says Dr. Yeu.

LipiFlow and intense pulsed light are the newest treatment options for dry eye. Dr. McDonald says that LipiFlow has a high conversion rate in her practice. "It is a 12-minute computer-controlled pulsating thermal lid massage treatment that is highly effective in treating dry eye," she says. "The LipiFlow treatment is not covered by insurance, so—for the average practice with the average LipiFlow pricing structure—the margins are usually at least as good as if the surgeon performed a LASIK procedure. Another advantage to the LipiFlow treatment is that there is just about no medicolegal liability with it; I have never heard of a LipiFlow lawsuit because it is so non-invasive."

Jay Pepose, MD, PhD, medical director of Pepose Vision Institute and president of the Lifelong Vision Institute in St. Louis, notes that LipiFlow should not just be considered as a last-resort treatment option. "The patients who are trying LipiFlow as a last resort are the most motivated, but you have to be careful with them because if you have someone with no meibomian gland function, those patients are so end-stage that they may not respond to the treatment. It is always better to catch people before end-stage, while they still have some functional glands," he says.

Another procedure used to treat dry eye is intense pulsed light, or IPL. "I like the concept but there is very little published about it compared to how much is published about other treatments, such as LipiFlow," Dr. McDonald says. "There is a little more liability with IPL, so you have to be careful:

800.735.0357
haag-streit-usa.com

LEGENDARY IS MATERIALISTIC

14-ply birch. Forged iron. Tough, hand-sewn upholstery. These are the materials of a legend. Built into our ultra-durable exam chairs and stands to make them last for decades. And they're virtually maintenance free.

Call us materialistic. We're okay with that. Because it's what makes Reliance Medical Products Brutishly Durable Since 1898.

Find your legendary exam chair and instrument stand at **reliance-medical.com**, or call 800.735.0357.

The Superior Practice.

RELIANCE INTERNATIONAL

Patients who are more darkly pigmented can get scarring, and one has to remember to insert the eye shields or there can be ocular damage."

Adding new treatment options can disrupt patient flow, so you may want to consider grouping dry-eye patient visits. "When we first started offering LipiFlow, when a patient said he or she wanted it, we were doing it right that very moment," Dr. McDonald says. "However, this made patient flow a bit chaotic. Because it is a 12-minute procedure, we decided to have 'Dry-eye Fridays.' We do LipiFlow treatments all day on Fridays. We have now trained our optometrists to perform LipiFlow procedures, but we did them ourselves until we felt we had done enough to be totally comfortable with these treatments."

The Bottom Line

Other ways to increase income include tear osmolarity testing and taking anterior segment images. "The Keratograph 5M by Oculus has—in addition to a Placido-based topographer—five new images that assist in the diagnosis of dry eye and meibomian gland disease and the response to treatment," Dr. McDonald says. "For instance, it has an automated tear breakup time, which is notoriously difficult to measure by clinical observation only. Not only does it tell you what the tear breakup time is, but it shows you what part of the cornea broke up first. It will give you the average breakup time in seconds and will classify the level of dry eye. It also has meibography, so the glands can be seen and the gland-containing area of the lid can be calculated, as well as demonstrating gland tortuosity and documenting where on the lid the dropout is occurring. It also has a way to categorize conjunctival erythema by calculating the ratio of blood vessels to sclera. It will accurately and automatically stage conjunctival erythema for the clinician, so it takes away the subjectivity of staging 'redness.' "

Table 3. Osmolarity Testing Scenario

Number of patients		1,500
Number of eyes tested		2
Number of visits		4
Number of osmolarity tests		12,000
Reimbursement per eye	$23.40	$280,800
Cost of TearLab Osmolarity System (Free use of system with Test Card Commitment)		$0
Cost of Test Cards	$10	$120,000
Net revenue of TearLab Osmolarity Testing (Does not include revenue for office visits, punctal plugs or supplement sales)		$160,000

Additionally, it determines the thickness of the lipid layer using interferometry, provides automatic measurement of the tear meniscus height, and tracks the movement of particles in the tear film to determine tear viscosity. "The practice can invoice for these photographs using the external photography CPT code, and the average reimbursement for these photos is $40," Dr. McDonald says.

To develop a dry-eye center of excellence, Dr. McDonald recommends starting with tear osmolarity first. "Get the doctors and staff comfortable with how to do it and when to do it. Once you have that under your belt, you should quickly move on to acquiring LipiFlow technology and the Keratograph 5M," she says.

However, be prepared for a big price tag. "The Keratograph 5M is approximately $25,000 to $28,000. The LipiFlow/LipiView package from TearScience is around $100,000," she says.

To defray these costs, Dr. Yeu says she has heard of practices that are collectively purchasing the fairly portable unit and are sharing the LipiFlow like a "timeshare," where the unit travels between the practices on a rotating schedule. "The machine can go to one practice one week and then to another practice the next week," she says. "Another great idea to help cover the overhead may be to consider offering your referring ophthalmologists and optometrists the option of bringing their patients over and allowing them to perform their own treatments."

Dr. Yeu believes that the use of LipiFlow to treat dry eye is on the rise. "Although it's still a relatively newer therapy and there is not as much out there in evidence-based literature to support this yet, we believe that the LipiFlow will likely grow in its indications," she says. "I would not be surprised to see this being utilized in all realms of mild to moderate dry-eye disease, not just for the obvious evaporative ones. In-office meibomian gland expression is going to be more and more widely utilized. It is like any other chronic disease in that there is no single modality therapy that is a cure-all. I think LipiFlow is a great adjunctive professional therapy that will continue to grow and gain greater momentum in the next few years and is certainly not a fad treatment."

Even if you are not interested in getting in this deep and purchasing expensive equipment, your practice can still capitalize by simply expanding your dry-eye patient base and following them. These added patients will also expand your surgical population as they later require cataract surgery or glaucoma treatment.

Bruce Maller, an ophthalmic business consultant, has developed a conservative dry-eye financial model *(See Tables 1 & 2)*. First, he provides an

example of a dry-eye patient's visits/charges for one year if a patient had the chief complaint of blurry vision. Visits alone would bring in $354 per patient per year. Additionally, if two punctal plugs were implanted, the revenue would be $219 per patient, and the revenue for four plugs is $370 per patient.

Then, he calculates the revenue and net income opportunity for a practice that was able to bring in 1,500 dry-eye patients, which is a conservative estimate according to Dr. McDonald. "Bruce assumes that with very modest marketing, it would be fairly easy for any practice to get 1,500 new dry-eye patients to come in over the course of a year," she says. "Based on several recent Gallup polls, Bruce was able to calculate how many cataract, glaucoma and retina cases would be found in those 1,500 dry-eye patients. He assumed that the ophthalmologist will only be able to keep half of them in the practice. Though Bruce used modest estimates in every instance, as well as 2012 Medicare reimbursement rates, it was staggering how profitable this effort—an emphasis on treating dry eye—was to the average practice. You don't have to stop treating cataracts or glaucoma or anything else; your volume of these cases will actually increase."

When tear osmolarity testing is added to the model, an additional $160,800 of net revenue is possible. *(See Table 3).*

Other Innovative Ideas

For additional income, Dr. Pepose's practice also sells some dry-eye products. "It is not terribly profitable but we have an optical, and the optical carries fish oil and different artificial tears," he says. "We try to carry some that you can't get too easily at the pharmacy. We want to have a good, non-preserved tear and a good, oil-containing tear. This also gets people into the optical, where they may make an additional purchase. Some practices are also initiating allergy skin testing, so we are looking into that because there is a lot of overlap in these patients between dry eye and allergy."

Dr. McDonald believes that it is the perfect time to get into this field because of the demographic shift in the population. In addition, there are better diagnostics, better drugs and better procedures for ocular surface disease. "We can do more for these patients than ever before, and with virtually no medicolegal exposure," she notes. REVIEW

REVIEW® of Ophthalmology

Ophthalmic Resources Online

This service allows you to capture needed measures for two meaningful use objectives:

1) electronic transmission of patient prescriptions

2) distribution of patient-specific education materials

ECP Resources and ePrescribing from *Review of Ophthalmology* and Healthcare Resources Online enable you to provide patient education, electronic prescribing and generate reports that allow you to attest for meaningful use incentives; however, determination of your bonus payments from CMS depends on other factors and qualifications specific to your practice.

For More Information, Visit Our MD E-Prescribing Resources Page:

www.revophth.com/MD_Resources_eRX/

Download a QR scanner app. Launch app and hold your mobile device over the code and get ready to view our website.

the Secret sauce to thriving in 2014

We're the only EHR with the *real* recipe.

ICD 10 Ready | Health Information Exchange Compatible | RAC Audit Protection | EHR Interopera-bility | Staff Training | Data Backup Services | Mobile Platform Access | Cloud-Based Solutions | Data Visual-ization | Eye Care Specific Workflow

Meaningful Use Stage 2 Certified

The rules for EHR providers have changed. Doctors who qualified for Meaningful Use Stage 1 will need to attest to MU Stage 2 during the 2014 calendar year.

Medflow is certified for Meaningful Use Stage 2. Industry insiders have estimated that 50% of current EHR systems will not make it through the Stage 2 and 3 certification processes[1]. Medflow will be here for you as the industry continues to evolve.

[1] Black Book Rankings 2013 Survey of EHR consultants, analysts, managers and support team members, www.blackbookrankings.com/healthcare/

Automated PQRS Reports

PQRS is a reporting program that uses a combination of incentive payments and payment adjustments to promote reporting of quality information by health care professionals. Medflow automates this reporting for doctors.

As EHR use grows, doctor transparency will become mandatory. Manually entering these reports is time-consuming, confusing, and at risk for human error.

Automated PQRS Reports ensure doctors receive every incentive payment they deserve for adopting and using EHR. This functionality is available in Medflow Stage 2 Certified software versions.

Integrated C3 Coding

C3 automates the patient visit coding process, using patient and visit data to ensure the correct code is entered, every time.

The healthcare system is increasingly built around rules, regulations, codes, and transparency. Ensuring you can code patient visits accurately and efficiently is vital.

C3 protects your practice from under-coding (resulting in lost revenue) and over-coding (resulting in possible penalties). The cumulative financial benefit of C3 for your practice revenue is 4%[2] - that means 4% more revenue safely in your pocket.

[2] Corcoran Compliance Connection, data on file

For more information log on to one of our Meaningful Use Stage 2 webinars.

October 28 ..... 5:00 PM EST
November 11 ..... 4:30 PM EST

visit www.medflow.com to register

Medflow Eyecare's Leading EHR Solution

AAO 2013 Booth 3313 • www.medflow.com • 855-MEDFLOW


Gene Therapy for Retinal Diseases

The eye represents a unique target organ for gene therapy. Here's a look at some of the current avenues of research.

J. Peter Campbell, MD, MPH, and J. Timothy Stout, MD, PhD, MBA, Portland, Ore.

Almost as long as we have known about our genetic makeup, scientists have dreamed of harnessing the power of gene expression to treat human disease.[1] It has taken many years to realize those dreams, however the past 10 years have led to some very promising advances.[2] Gene therapy, in its current form, employs the host's gene expression machinery to transcribe and translate therapeutic genetic information that has been delivered to target cells through the use of genetically modified viral vectors. One challenge of gene therapy has been our ability to design vectors able to introduce the therapeutic genes into host cells and achieve long-term gene expression without local toxicity or immune reaction.[3]

The eye represents a unique target organ for gene therapy due to the immune privilege afforded by the blood-ocular barrier, the ability to directly visualize, access and locally treat the target tissue and, with regards to clinical trials, the simultaneous control provided by the other eye. Perhaps it is not surprising, then, that one of the most publicized advances in the field in the last decade was a series of trials for Leber's congenital amaurosis type 2 (LCA2).[4-6] These pivotal trials paved the road for a number of other early clinical trials for retinal disease and the first Phase III study for gene therapy involving the eye. A full review of gene therapy techniques and preclinical research is beyond the scope of this article, and we would refer the reader to additional references.[2,7] In this brief review we would like to provide a broad overview of current avenues of research, focusing on those in or near clinical trials.

Inherited Retinal Degenerations

From the beginning, the idea of targeting inherited retinal degenerations has been tantalizing. It is simple in theory to imagine how, in diseases where the gene defect is known, the wild-type gene could be introduced with a viral vector and the functional gene product would restore function and/or prevent cell death. However, translating the theory into reality depends at least upon: a) the causative gene being known; b) the therapeutic gene being cloned into a viral vector; c) the vector being safe and able to transduce the appropriate cells; d) a sufficient potential patient pool to attract pharmaceutical support; and e) the underlying diseased retina having the potential for restoration of function with gene replacement and not being irreparably diseased.

Leber's congenital amaurosis is a heterogeneous group of autosomal recessive diseases characterized by early-onset rod-cone dystrophy and severe vision loss. There are a variety of genes that produce the LCA phenotype of varying severity, but certain defects in RPE65 produce LCA2 with early-onset blindness but delayed photoreceptor degeneration. This led investigators to hypothesize that restoration of function of RPE65, which is involved in photoreceptor cell cycling, might prevent progression of degeneration and may allow restoration of visual function.[3]

After encouraging preclinical animal studies, approval was obtained for human trials in 2008, and three separate Phase I trials demonstrated the safety and efficacy of RPE65 delivered via an adeno-associated virus vector by subretinal injection, with functional improvement beyond two years.[4-6,8]

This article has no commercial sponsorship.

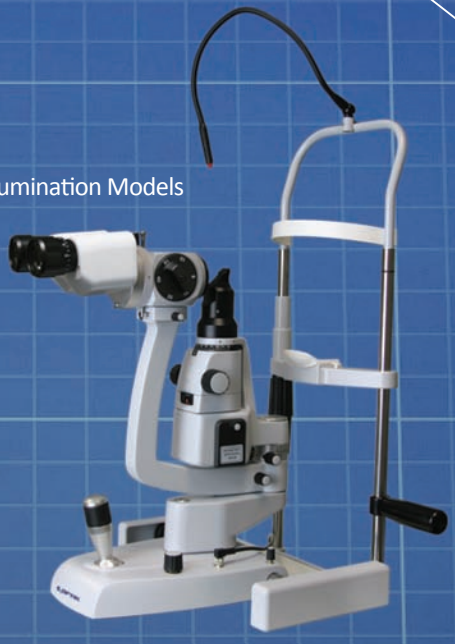
ANATOMY OF A GREAT EXAM LANE

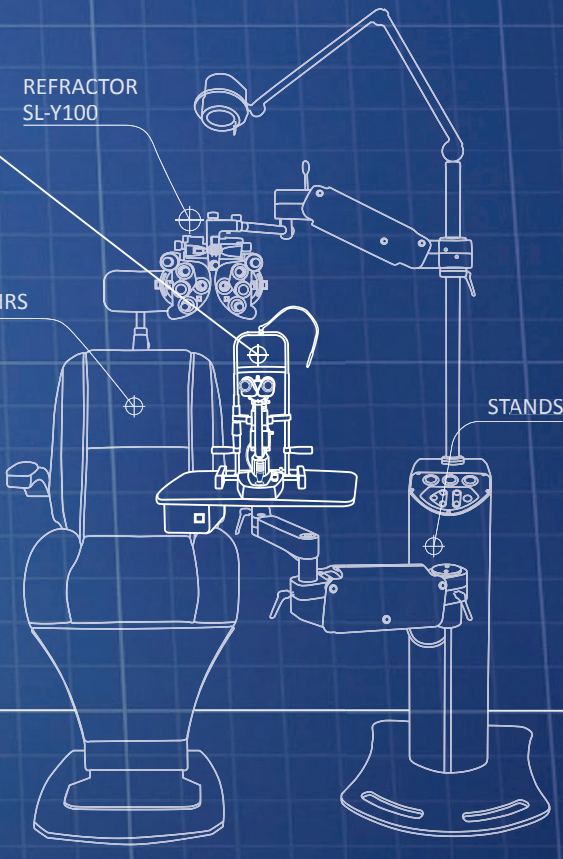
Quality or Value - go ahead you can have both

S4OPTIK products are the perfect blend of extraordinary Value and Quality. Instruments which satisfy even the most discerning practitioner.

H + Z SERIES SLIT LAMPS

Z-SERIES
Compact Illumination Models





H-SERIES
Vertical Illumination Models

SLIT LAMP FEATURES

- Multilayered anti-reflective coatings
- Stunning optical quality allowing clear visualization and depth of field
- 20% increase in optical transmission
- 10% increase to the depth of field

www.s4optik.com | info@s4optik.com

RIGHTMED S4OPTIK

5325 Cleveland Street, Suite 303.
Virginia Beach, VA 23462
T: 1.888.224.6012 I www.s4optik.com

TECHNOLOGY VALUE RELIABILITY

Gene Therapy Trials

Disease	Gene	Vector	Mode	Phase	Sponsor	Clinicaltrials.gov Identifier	Locations
Leber's congenital amaurosis type II	CBSB-RPE65	AAV2	Subretinal	I	University of Pennsylvania	NCT00481546	Children's Hospital of Philadelphia University of Florida
Leber's congenital amaurosis type II	RPE65	AAV2	Subretinal	I/II	Nantes University Hospital	NCT01496040	Nantes University Hospital
Leber's congenital amaurosis type II	CB-RPE65	AAV2	Subretinal	I/II	Applied Genetics Technologies Corp	NCT00749957	Casey Eye Institute, Oregon Health & Science University University of Massachusetts
Leber's congenital amaurosis type II	RPE65	AAV2	Subretinal	I/II	Children's Hospital of Philadelphia	NCT01208389	Children's Hospital of Philadelphia
Leber's congenital amaurosis type II	RPE65	AAV2	Subretinal	III	Children's Hospital of Philadelphia	NCT00999609	Children's Hospital of Philadelphia University of Iowa
MERTK-associated retinitis pigmentosa	VMD2-MERTK	AAV2	Subretinal	I	King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia	NCT01482195	King Khaled Eye Specialist Hospital
Neovascular age-related macular degeneration	Endostatin & Angiostatin	LV	Subretinal	I	Oxford Biomedica	NCT01301443	Wilmer Eye Insitute, Johns Hopkins Hospital Casey Eye Institute, Oregon Health & Science University
Neovascular age-related macular degeneration	SFLT01	AAV2	Intravitreal	I	Genzyme	NCT01024998	Johns Hopkins Hospital Retina Consultants of Arizona Ophthalmic Consultants of Boston University of Massachusetts
Neovascular age-related macular degeneration	SFLT-1	AAV2	Intravitreal	I/II	Lions Eye Institute, Perth Avalanche Biotechnologies	NCT01494805	Lions Eye Institute, Perth, Australia
Choroideremia	REP1	AAV2	Subretinal	I/II	University of Oxford	NCT01461213	Moorfields Eye Hospital St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust Oxford Radcliffe Hospitals NHS Trust Eye Unit, Southampton University Hospitals NHS Trust
Stargardt's disease	ABCR	LV	Subretinal	I/II	Oxford BioMedica	NCT01367444	Casey Eye Institute, Oregon Health & Science University Centre Hospitalier Nationale d'Ophthalmologie des Quinze-Vingts
Usher type IB	MYO7A	LV	Subretinal	I/II	Oxford BioMedica	NCT01505062	Casey Eye Institute, Oregon Health & Science University

There are several ongoing Phase I, II and III studies in the United States and Europe for LCA2 using a variety of vectors and protocols to treat LCA2, and many believe Food and Drug Administration approval is possible.[9]

Though the initial clinical results have been encouraging and have led to improvements in visual function lasting several years, there is evidence that the underlying retinal degenerative process in LCA2 may not be slowed by the delivery of RPE65. Artur Cideciyan, PhD, and colleagues recently demonstrated continued photoreceptor degeneration after therapy at a rate consistent with the natural history of LCA2.[10] These results affirm the need for long-term clinical studies of these therapies, and for ongoing research aimed at slowing the kinetics of the underlying degeneration, which may be perpetuated by "downstream" processes unaffected by delivery of the gene product.[11]

Several other inherited retinal degenerations are in early-phase clinical

PSF Integra™

Complete, Subjective Refraction Lane-in-a-Box!

Vmax Vision is pleased to offer another ground breaking product, the PSF Integra™. Combining the subjective PSF Refractor™ with a uniquely compact design ensures the highest level of accuracy and minimized footprint. The PSF Integra™ provides practice benefits such as:

- Maximize efficacy and productivity – Now, a small, 5'x5' space can function as a 20' lane!
- No accommodative response – The PSF Integra's effective target distance is 20 feet
- Increased visual acuity – Utilizing advanced Point Spread Function technology, patients see beyond 20/20, routinely achieving 20/16 or 20/12
- 5X more precise than the phoropter – The advanced PSF Integra™ Rx helps ensure patients will fill their prescription with your practice
- Subjective night vision refraction – New treatment modality and new revenue
- Deliver maximized quality of vision – Combine the ultra precise PSF Integra™ refraction with customized Encepsion™ Lenses

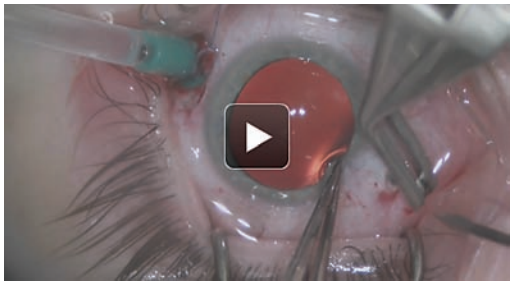
See a demonstration of the PSF Refractor™ and PSF Integra™ at **AAO (Opthalmology)** Booth 1012 or at the following Optometry shows: **VEW** in Booth LP10069, **EastWest Eye Conference** in Booth 422, **OAOP**, and **AAO (Optometry)** Booth 1022.

For an in-office demonstration, please call: 888.413.7038 or visit: www.vmaxvision.com.

vmax™
VISION, INCORPORATED

1.888.413.7038
www.vmaxvision.com

trials using a number of different viral vectors, including choroideremia, autosomal recessive retinitis pigmentosa, Stargardt's, and Usher syndrome (type IB), with many others in preclinical animal studies. Most of the clinical work involves transduction with AAV or lentiviral vectors. Currently, the long-term LCA animal model data suggests ongoing production of RPE65, but there is no regulation of the kinetics of the gene production. For LCA2, this may not matter, but for other disease states, retinal function may be more sensitive to the "therapeutic index" of the gene product.



For a brief video of gene therapy delivery to the retina, please visit revophth.com/video/gene/.

Broader Applications

While the success of the LCA2 trials demonstrated proof of principle that a deficient single gene could be delivered to the eye and restore function, and brought hope to many patients with inherited retinal disease for whom there has been no available treatment, designing gene therapy vectors for monogenetic recessive conditions requires a large amount of resources for a relatively small potential patient population. Bringing the cost of this technology down enough to encourage exploration into rarer inherited retinal degenerations may require a broader potential market overall. It is exciting to explore how this technology could be used to help restore or preserve vision for more common conditions.

Age-related macular degeneration is a leading cause of irreversible blindness in the United States and is increasing in prevalence. Though the pathophysiology of AMD is complex and multifactorial, the mainstay of treatment for the neovascular form is vascular endothelial growth factor inhibition, which currently requires monthly evaluation and repeat intravitreal injections. Though this represented a breakthrough in the treatment of this disease, the frequency of required injections is burdensome and expensive. Myriad preclinical studies have explored other growth factors involved in the pathogenesis of neovascular AMD and other delivery models, including subretinal injection, subconjunctival injection, intravitreal injection of longer-acting molecules and intraocular delivery devices.[12,13]

Peter Campochiaro, MD, and colleagues demonstrated safety in a Phase I study of pigment epithelial derived factor (PEDF) in an adenoviral vector with intravitreal injection. They demonstrated a dose-dependent clinical response with tolerable local side effects.[14] Another Phase I trial using an AAV vector to express a soluble VEGF receptor is currently enrolling patients.[15]

Besides VEGF, PEDF and placental growth factor, other molecules such as endostatin and angiostatin modulate the permeability of the retinal and choroidal vasculature and represent intriguing targets for gene therapy. A Phase I study of subretinal injection of a lentiviral vector-expressing endostatin and angiostatin is currently enrolling patients with advanced neovascular AMD.[14] Another trial involves the use of an AAV vector to deliver a soluble form of the VEGF receptor into the eyes of similar patients.[15] These are landmark trials of drugs that may ultimately replace monthly therapeutic injections for patients with neovascular disease.

Retinal vascular disease, including diabetic retinopathy and retinal vein occlusions, represents another large target population with numerous molecular targets for gene therapy. As in AMD, VEGF inhibition with monthly intravitreal injection has become the mainstay of treatment for macular edema due to diabetes and vein occlusion, and clinical trials are under way exploring the role of VEGF inhibition in retinal neovascularization in proliferative diabetic retinopathy. In both AMD and diabetic macular edema, monthly injections are often required for months to years, and lapses in treatment can lead to further vision loss. There are currently no clinical trials for gene therapy in retinal vascular disease.

Future Directions

There are prospects for commercially available gene therapies for retinal disease in the near future, but much work remains to be done. In the field of inherited retinal degenerations, the next step will be to expand the indications available for treatment, and initiate treatment earlier in the disease process, which will require excellent safety and efficacy data in the current and future clinical trials.

Similarly, in AMD and retinal vascular disease, where we have increasingly effective therapies, the safety of long-term, viral-vector-mediated gene transduction will need to be demonstrated. Especially for conditions that have existing therapies, the cost of gene therapy will need to be justified. In a culture of ever-increasing healthcare costs, the novelty and intrigue of new technology must be balanced with thoughtful cost-effectiveness analysis.

Finally, it remains to be seen whether gene therapy may be used in conjunction with, in place of, or will be replaced by cell-based regenerative therapies on the horizon.[16] One thing is certain: For thousands of patients

(continued on page 81)

All Pupil II

Vantage Plus

Spectra Iris

Vantage Plus
Digital

Get a
Free Keeler Indirect
When You
Buy Any 3 Keeler Indirects,
& Trade-In Any 3 Indirects
through December 31, 2013

Learn more at www.keelerusa.com

For years, we've been telling you that Keeler* is the world leader in innovation, technology, and market share.

- *First Wireless Indirect*
- *First LED indirect*
- *First Digital Indirect*
- *First Intelligent Optical System*
- *Patented Hi-Mag Lens*

Buy Online!
keelerusa.com

Keeler
OPTICS

*iData Research Inc. 2011 – "Keeler Instruments was the leading competitor in the U.S. market for BIOs with a share of 63.6%.". "The binocular indirect ophthalmoscope market has seen a great deal of innovation over the years. Keeler Instruments has been at the forefront of this innovation".

Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008 • Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

The Modern Wisdom Of Clinical Models

How models of disease, carried out in the clinic, can yield useful information about an ailment and treatments for it.

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

The perceptive thinker Hippocrates famously declared, *"Vita brevis, Ars longa, Occasio praeceps, Experimentum periculosum, Iudicium difficile,"* or, "Life is short, art long, opportunity fleeting, experiment perilous, judgment difficult." When you think about it, this could be aptly applied to nearly all circumstances in medicine. In our short lifespan, we are physicians with a craft, a skill that takes a lifetime to acquire and hone, and despite our training and experience we face difficult diagnostic and treatment decisions on a daily basis.

How would this aphorism stand up to the study of therapeutics and their development? Just as well. While the history of medicine is full of perilous trial-and-error discoveries of therapies, in the 20th century and beyond our approach has been more selective, more precise, and more able to predict a response at onset of treatment as well as monitor the duration of its action. To do this, drug development methods need to distill the disease to its essence in a discrete time frame where clinically and statistically significant effects can be compared to an active or negative control.

The modern approach to drug discovery rests on the foundation of randomized, double-masked clinical trials in predefined disease populations, yet the nature of certain diseases sometimes makes defining a drug effect extremely difficult. In these cases, a clinical model that mimics the disease may provide a superior platform for investigating the activity of drugs in a clinical setting. Those diseases that are best served by a model include conditions with: 1) a strong subjective component with regard to symptoms; 2) inherent temporal, locational and behavioral variability, both between and within subjects; and 3) significant placebo efficacy. In ophthalmology, two such diseases are ocular allergy and dry eye.

Moving Targets

To describe the utility of modeling, let's first drill down on the characteristics of each of these diseases. With the exquisitely sensitive cornea to reckon with, ocular surface diseases are all defined by ocular pain or discomfort. Itching is the pathognomonic symptom of allergic conjunctivitis, while other allergy symptoms, including tearing and swelling, have subjective components that are halfway between a sign and symptom.[1] In contrast, dry-eye disease has a plethora of symptoms related to us by the patient: dryness; scratchiness; grittiness; burning; stinging; itching; ocular fatigue; and, rarely, photophobia. How can a clinician accurately measure the daily incidence and severity of these subjective symptoms? The subject diary has been the conventional method of collecting subjective data outside of the clinic, but it is fraught with inconsistencies and, when it is completed, is often done so cursorily in the parking lot just before the doctor's visit. The elegance of a disease model in this setting lies in the fostering of symptoms' appearance directly in the presence of the clinician, who no longer has to jog the patient's memory to retrieve an accurate recapitulation of the disease process. This is a reverse case of "now you have it, now you don't," in which consistent, reproducible, real-time subject grading provides invaluable data on how a drug can alter disease symptoms.

The second disease characteristic

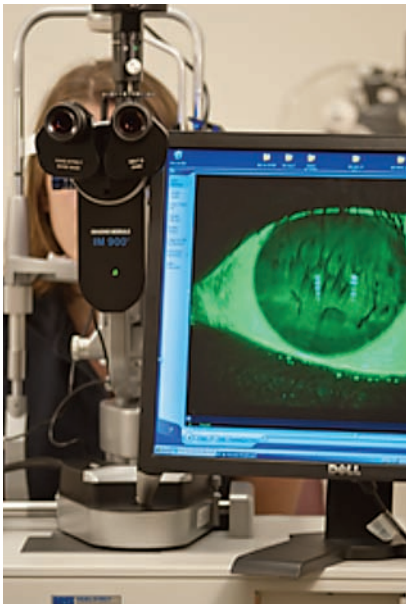
This article has no commercial sponsorship.

that benefits from a modeling approach is variability. Allergic sensitivity is highly variable between individuals: Patients may experience anything from mild itching or rhinorrhea to off-the-chart IgE levels and risk of anaphylaxis. Similarly, dry-eye disease can run the gamut from mild irritation due to prolonged visual tasking (such as a day in front of a computer screen) to a debilitating level of corneal abrasion, pain and photophobia. With such diversity in the patient population, it's likely that responses to a potential therapeutic will also be varied.

Using a clinical model it's possible to identify a potential study group with disease severity that's not so mild or so severe that a drug effect cannot be readily observed. In addition, subjects with a similar, moderate severity of disease are more likely to display a clinically significant magnitude of response to an effective therapy. In this way models allow us to reduce the noise inherent in a variable disease and provide a true measure of a treatment's clinical value.[2-4]

Temporal variability is also a common feature of many diseases. Is the disease worse or better in the morning or evening? Does it subside at night? In the case of allergy, two possibilities are common. Allergy sufferers who are sensitive only to airborne pollens will be less symptomatic in the evenings while in bed (with eyes closed) away from exposure. This is also true for dry-eye sufferers with their lids closed, allowing the ocular surface time to reset tear-film imbalances and avoid the high cost of tear evaporation. In contrast, a subject with mite allergies might find bedtime to be his worst nightmare when it comes to allergic symptoms.

The dry-eye patient generally feels good in the morning, after the ocular surface has been protected throughout the night, and progressively worsens with time awake.[5] This observation highlights the importance of noting and controlling for the time of office appointments when doing a clinical trial, as a dry-eye subject will be much more naturally symptomatic at an evening appointment. A second form of temporal variability involves the seasons: Is the disease characterized by seasonal fluctuations? Pollen allergies are an obvious example of this, but the worsening of dry-eye symptoms in the low humidity of indoor winter environments is another seasonal accent to this complex disease.



Traditional diagnostics such as tear-film breakup can be automated for use in clinical trials.

The third type of disease variability is locational. Geographic differences in ocular surface disease incidence or severity are typically due to differences in climate: Arid regions are worse for dry eye while temperate climates and long growing seasons can exacerbate pollen sensitivities. There's also growing evidence that urban pollution contributes to both chronic dry eye and allergic inflammation.[6-8] On the opposite end of the spectrum, the absence of dust mites at higher elevations can provide a needed respite to both allergy and asthma sufferers.

Locational variability is far more difficult to control in a clinical setting, however. A person in today's world typically moves between four or more distinct environmental settings: the home; public or private transportation; the workplace; and various outdoor or public spaces between the others. Each of these environments has its own level of pollutants, pollen and other potential allergens, and its own characteristic relative humidity, temperature, ventilation and lighting. All of these factors can affect the signs and symptoms of dry eye or ocular allergy. Similarly, the drastic changes in environment and location that may occur on weekends can also greatly alter a person's disease, be it freedom from reading, writing and staring at a computer eight hours a day for a dry-eye sufferer, or outdoor activities like hiking or cycling for the pollen allergy sufferer. This behavioral variation adds an additional layer to the complexity of tracking ocular surface disease process and treatment.

It's important to remember that all these types of variability are uncontrolled and uncontrollable not only across subjects (inter-subject variability), but also within subjects (intra-subject variability), creating a situation of waxing and waning signs and symptoms without consistency, a highly variable signal that can make the identification of a drug effect difficult or impossible.

The Placebo Effect

The difficulty in conducting reliable clinical trials is impeded further when signs and symptoms respond to placebo treatment. In some conditions, the placebo in a topical drug trial may be similar to the current treatments used by trial subjects. For dry-eye treatment trials, the majority of subjects are already using tear substitutes *ad lib*, and while they may only provide transient symptomatic

relief they are, for many patients, the best available therapy. Nevertheless, a negative control is needed to compare efficacy across double-masked, randomized, placebo-controlled trials. This is usually provided by the drug vehicle, whose comfort, particularly in the case of dry eye, is maximized in terms of osmolarity and wettability. It is highly predictable, then, that this vehicle will provide significant benefit to dry-eye sufferers used to treating their disease with tear substitutes.

Placebo effects also impact ocular allergy trials, although their effect is a bit more complex. Tear substitutes or vehicle placebo can provide multiple benefits to the allergy sufferer and thus confound clinical trial findings. They wash away environmental allergens, minimizing their contact with surface antibodies and mast cells. They also dilute the in-place mediators released by previous exposure, including histamine, prostaglandins, leukotrienes, chemokines and cytokines. Finally, the wettability effects of topical placebos provide comfort and relief from ocular surface damage and inflammation, even in the absence of the well-known comorbidity of allergy and dry eye,[6] leading to decreased symptomology.[9] With these obstacles to overcome, it's a wonder that any drug has been approved based on environmental studies.

Of course, use of models in ocular surface drug development is a subject we've been involved in for quite some time.[10] Now that we've described some of the general factors involved in the decision to use a model-based protocol to test drug efficacy, let's take a closer look at the specific aspects of two models that we have designed and refined to respond to each of these impediments to well-founded and reproducible clinical science.

Conjunctival Allergen Challenge

While the instillation of allergen to the eye has been performed for decades to study allergic disease, the fine control that has evolved in every aspect of this protocol has led to the approval of 19 anti-allergic drugs since its acceptance as a validated method for drug development in 1990.[10]

In the CAC, pre-selected subjects with a history of ocular allergy and a positive skin test are administered baseline challenges on two separate visits with the allergen to which they are sensitized, establishing a reproducible, and consistent, bilateral response of moderate severity to a pre-determined dose. The step-wise increases in allergen also bring all subjects to approximately the same reaction, avoiding the large fluctuations caused by differences in sensitivity. Subjects can then be administered drug in the prescribed dosage regimen in a double-masked, randomized, placebo-controlled fashion. While this might appear to be prevention rather than treatment of an allergic response, the Food and Drug Administration accepts this method since it reflects the nature of allergic disease, which is actually episodic bursts of mediator release in response to exposure, and whose treatment can be seen as a temporary breach in these episodes. After drug treatment, the subject is again challenged and signs and symptoms are graded with scales developed in the past 25 years that are tailored to the nuances of itching, redness and swelling specific to allergy. The itching scale in particular allows the subject to grade his or her symptoms in front of the clinician with confidence that data are being collected in real time.[9-11]

This challenge method identifies effects at onset, and also the duration of effect, which is almost impossible to ascertain under natural conditions. Thus, the CAC model creates a discrete allergic reaction in all subjects in-office, under clinically observable conditions. In this way, variability originating from inherent differences in allergic sensitivity, time of day, season, location and behavior are all minimized. With these variables taken care of, the beneficial effects of placebo are reduced and a true drug effect can be accurately defined.[11]

The CAE Model

The ocular surface is exquisitely in tune with its environmental conditions, and manipulation of factors such as temperature, wind or relative humidity can provide a means to induce tear-film instability and a desiccating stress on the ocular surface. In the controlled adverse environment, subject responses to an adverse environment challenge while performing a visual task are used as a baseline, and aid in identifying a defined population of subjects with comparable disease signs and symptoms. Like the CAC, the CAE can also be used to assess test-agent efficacy by measuring changes in the dry-eye status of subjects from baseline to post-challenge through slit lamp evaluations, validated scoring of dry-eye redness by the investigator and by computer,[12] staining with fluorescein and lissamine, tear-film breakup times[13] and Schirmer's testing. The subject's symptomology is graded individually and with a variety of validated grading systems, again in a clinical setting and in real time, preventing the vagaries of diary completion and with no hindrance from subjective memory. Finally, precise methods have been developed to assess blink behavior,[14,15] tear-film dynamics (OPI)[16] and visual function during tasking (IVAD),[17] all of which can be combined with CAE challenge in a before-and-after protocol. Often, CAE challenge-based studies are conducted in concert with environmental collection of data, since treatment with active dry-eye molecules typically requires treatment durations of

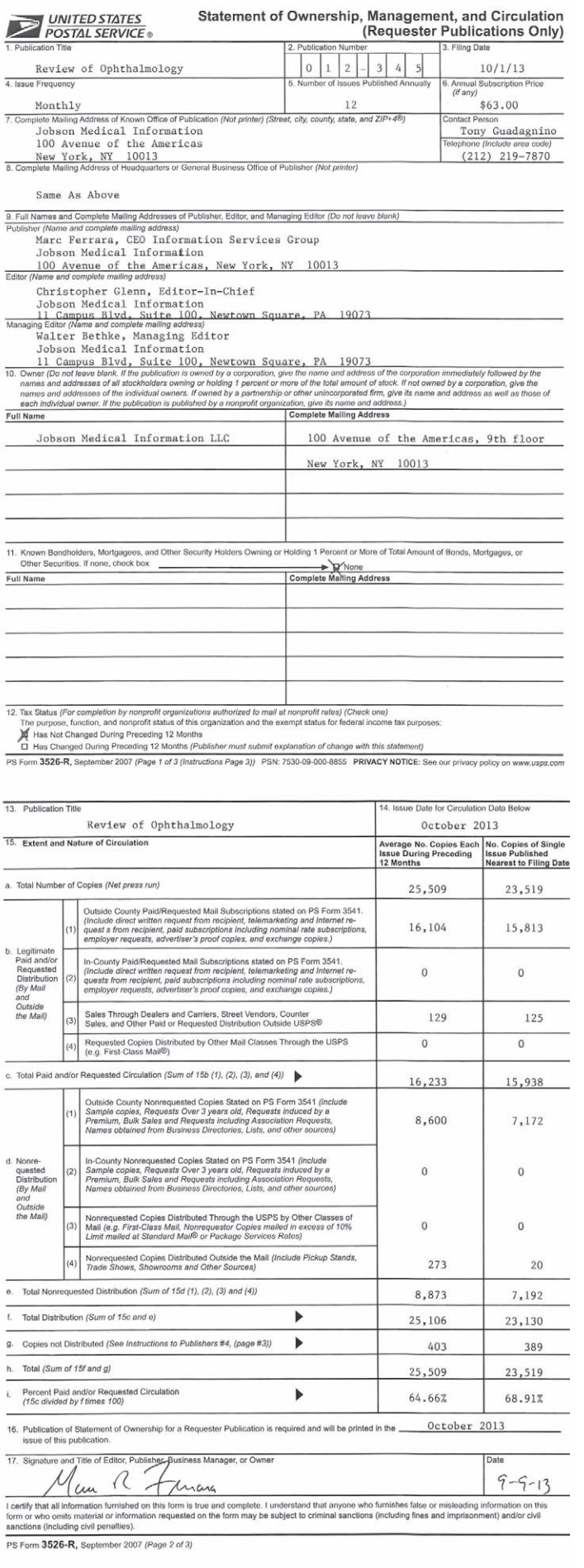
one month or more. Like the CAC model, the CAE model minimizes the inter- and intra-subject variability of inherent disease, environment and behavior. This dampening of background noise again aids in minimizing the beneficial effects of placebo when evaluating a drug.[2-4,9-11]

Overall, models allow us to focus on the potential efficacy of test compounds in shorter, more defined time frames. This allows for a streamlining of the development process with benefits to both the developers and consumers alike. Even when there is a desire for large-scale trials using more traditional protocols, disease models can provide vital proof-of-concept findings to speed the best therapeutics to the patients.

Though it's true "life is short and art long," is it possible that clinical models have let us sidestep the ancient wisdom, the idea of advancements in medicine evolving in incremental steps over time? Or have we simply seized the fleeting opportunity to test clinical science with the tools available today, based on a foundation of knowledge built over centuries? Medicine and clinical science have unquestionably benefited from disease models, which provide the opportunity for the experiment and judgment of Hippocrates with the velocity and precision that today's fast-paced society requires. REVIEW

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

1. Leonardi A, Bogacka E, Fauquert JL, et al. Ocular allergy: Recognizing and diagnosing hypersensitivity disorders of the ocular surface. Eur J Allergy Clin Immunol 2012;67:1327-1337.
2. Ousler GW III, Gomes PJ, Welch D, Abelson MB. Methodologies for the study of ocular surface disease. Ocul Surf 2005;3:3:143.
3. Abelson MB, Knight E. Dry eye therapy: Evaluation of current directions and clinical trials. Adv Exp Med Biol 1994;350:431-6.
4. Abelson MB, Ousler GW III, Nally LA, Emory TB. Dry eye syndromes: Diagnosis, clinical trials and pharmaceutical treatment-'improving clinical trials'. Adv Exp Med Biol 2002;506(B):1079-86.
5. Walker PM, Lane KJ, Ousler GW III, Abelson MB. Diurnal variation of visual function and the signs and symptoms of dry eye. Cornea 2010;29:6:607-12.
6. Gomes PJ, Ousler GW III, Welch DL, Smith LM, Coderre J, Abelson MB. Exacerbation of signs and symptoms of allergic conjunctivitis by a controlled adverse environment challenge in subjects with a history of dry eye and ocular allergy. Clin Ophthalmol 2013;7:157-65.
7. Barnes CS, Alexis NE, Bernstein JA, et al. Climate change and our environment: The effect on respiratory and allergic diseases. J Allergy Clin Immunol Pract 2012;1:2:137-141.
8. Warm K, Lindberg A, Lundback B, Ronmark E. Increase in sensitization to common airborne allergens among adults: Two population-based studies 15 years apart. Allergy Asthma Clin Imunol 2013;9:1:20.
9. Abelson MB, Loeffler O. Conjunctival allergen challenge: Models in the investigation of ocular allergy. Curr Allergy Asthma Rep 2003;3:4:363-8.
10. Abelson MB, Chamber WA, Smith LM. Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. Arch Ophthalmol 1990;108:1:84-8.
11. Abelson MB. Comparison of the conjunctival allergen challenge model with the environmental model of allergic conjunctivitis. Acta Ophthalmol Scand Suppl 1999;228:38-42.
12. Rodriguez JD, Johnston PR, Ousler GW 3rd, Smith LM, Abelson B. Automated grading system for the evaluation of ocular redness associated with dry eye. Clin Ophthalmol 2013;7:1197-1204.
13. Abelson MB, Ousler GW 3rd, Nally LA, Welch D, Krenzer K. Alternative reference values for tear film break up time in normal and dry eye populations. Adv Exp Med Biol 2002;506(B):1121-5.
14. Johnston PR, Rodriguez J, Lane KJ, Ousler G, Abelson MB. The interblink interval in normal and dry eye subjects. Clin Ophthalmol 2013;7:253-9.
15. Rodriguez JD, Ousler GW III, Johnston PR, Lane K, Abelson MB. Investigation of extended blinks and interblink intervals in subjects with and without dry eye. Clin Ophthalmol 2013;7:337.
16. Ousler GW III, Hagberg KW, Schindelar M, Welch D, Abelson MB. The Ocular Protection Index. Cornea 2008;27:5:509-13.
17. Torkildsen G. The effects of lubricant eye drops on visual function as measured by the Interblink Interval Visual Acuity Decay test. Clin Ophthalmol 2009;3:501-506.



UNITED STATES POSTAL SERVICE®

Statement of Ownership, Management, and Circulation (Requester Publications Only)

1. Publication Title	2. Publication Number	3. Filing Date
Review of Ophthalmology	0 1 2 - 3 4 5	10/1/13
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price (if any)
Monthly	12	$63.00

7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4®)
Jobson Medical Information
100 Avenue of the Americas
New York, NY 10013
Contact Person: Tony Guadagnino
Telephone (Include area code): (212) 219-7870

8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer)
Same As Above

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank)
Publisher (Name and complete mailing address)
Marc Ferrara, CEO Information Services Group
Jobson Medical Information
100 Avenue of the Americas, New York, NY 10013
Editor (Name and complete mailing address)
Christopher Glenn, Editor-In-Chief
Jobson Medical Information
11 Campus Blvd, Suite 100, Newtown Square, PA 19073
Managing Editor (Name and complete mailing address)
Walter Bethke, Managing Editor
Jobson Medical Information
11 Campus Blvd, Suite 100, Newtown Square, PA 19073

10. Owner (Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)

Full Name	Complete Mailing Address
Jobson Medical Information LLC	100 Avenue of the Americas, 9th floor New York, NY 10013

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☒ None

Full Name	Complete Mailing Address

12. Tax Status (For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☒ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months (Publisher must submit explanation of change with this statement)

PS Form **3526-R**, September 2007 (Page 1 of 3 (Instructions Page 3)) PSN: 7530-09-000-8855 **PRIVACY NOTICE:** See our privacy policy on www.usps.com

13. Publication Title	14. Issue Date for Circulation Data Below
Review of Ophthalmology	October 2013

15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies (Net press run)			25,509	23,519
b. Legitimate Paid and/or Requested Distribution (By Mail and Outside the Mail)	(1)	Outside County Paid/Requested Mail Subscriptions stated on PS Form 3541. (Include direct written request from recipient, telemarketing and Internet request s from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)	16,104	15,813
	(2)	In-County Paid/Requested Mail Subscriptions stated on PS Form 3541. (Include direct written request from recipient, telemarketing and Internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid or Requested Distribution Outside USPS®	129	125
	(4)	Requested Copies Distributed by Other Mail Classes Through the USPS (e.g. First-Class Mail®)	0	0
c. Total Paid and/or Requested Circulation (Sum of 15b (1), (2), (3), and (4)) ▶			16,233	15,938
d. Nonrequested Distribution (By Mail and Outside the Mail)	(1)	Outside County Nonrequested Copies Stated on PS Form 3541 (Include Sample copies, Requests Over 3 years old, Requests Induced by a Premium, Bulk Sales and Requests including Association Requests, Names obtained from Business Directories, Lists, and other sources)	8,600	7,172
	(2)	In-County Nonrequested Copies Stated on PS Form 3541 (Include Sample copies, Requests Over 3 years old, Requests Induced by a Premium, Bulk Sales and Requests including Association Requests, Names obtained from Business Directories, Lists, and other sources)	0	0
	(3)	Nonrequested Copies Distributed Through the USPS by Other Classes of Mail (e.g. First-Class Mail, Nonrequestor Copies mailed in excess of 10% Limit mailed at Standard Mail® or Package Services Rates)	0	0
	(4)	Nonrequested Copies Distributed Outside the Mail (Include Pickup Stands, Trade Shows, Showrooms and Other Sources)	273	20
e. Total Nonrequested Distribution (Sum of 15d (1), (2), (3) and (4))			8,873	7,192
f. Total Distribution (Sum of 15c and e) ▶			25,106	23,130
g. Copies not Distributed (See Instructions to Publishers #4, (page #3)) ▶			403	389
h. Total (Sum of 15f and g)			25,509	23,519
i. Percent Paid and/or Requested Circulation (15c divided by f times 100) ▶			64.66%	68.91%

16. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the October 2013 issue of this publication.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner — Date: 9-9-13

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

PS Form **3526-R**, September 2007 (Page 2 of 3)


The Forgotten Piece in The Compliance Puzzle

Getting your glaucoma patients to come in as recommended may be just as important as proper medication use.

Shan C. Lin, MD, San Leandro, Calif., and Kuldev Singh, MD, MPH, Stanford, Calif.

Every doctor managing glaucoma knows that compliance is a significant factor in how well patients respond to treatment. However, two types of compliance can affect the outcome: compliance with medication use—the type of compliance that has been the focus of much work and discussion—and compliance with recommended follow-up visits.

Hundreds of papers about medication compliance have been published. In contrast, little has been written about the impact of appropriate surveillance on disease outcomes. Recent data, however, shows that patient compliance with follow-up—returning for exams at the times prescribed by the doctor—may be at least as important as how faithfully the patient uses prescribed medications.

Here, we'd like to share some of the surprising findings recent studies have uncovered, and discuss the implications for clinicians striving to achieve the best possible outcomes.

The Power of Follow-up

Our group has been fortunate enough to have access to both medication refill and follow-up data on the same patients for whom disease progression has been monitored at San Francisco General Hospital. We hypothesized that how well glaucoma patients do over time might not simply be a question of whether or not they are taking their medications, but also how closely they are being monitored. Regular follow-up allows determination of disease course with adjustment of medications, as well as consideration of laser and surgical options for those who are doing poorly with current therapy.

While taking appropriate medications as prescribed likely improves outcomes, such therapy has its limitations; not all compliant patients are destined to do well. Making the assumption that medication compliance insures good outcomes, and placing insufficient emphasis on appropriate follow-up, can lead to disaster. Given that glaucoma is often an asymptomatic disease until late in the disease course, patients who forget to return to your office—perhaps assuming that simply taking the medications is enough—might be getting worse without knowing it.

Our most recent study was done in two parts. The first author of both reports was Cindy Ung, a medical student at Stanford University who performed a cross-sectional analysis on patients at San Francisco General Hospital. To determine subjects' level of disease we used classifications of glaucoma severity based on the American Academy of Ophthalmology's *Preferred Practice Patterns*. For purposes of determining compliance with medication use, we examined the patient's refill history using a previously validated method.

The first paper looked at medication adherence among glaucoma patients.[1] It found that patients who had more severe glaucoma were more compliant with medical therapy than those with mild or moderate stages of disease, as indicated by a greater propensity to refill their prescriptions *(See Table 1)*. (These results contradict a previous study that found that patients who were more diseased were less compliant with their medications.[2])

One possible explanation for these findings is that people who have more severe disease probably receive more counseling and are more aware of

Invest In Your Practice And Get A Guaranteed Positive Return.

Lombart's CS-4 Package Offers Quality, Style & Value.

Ask about optional Slit Lamp & Chart Projector configurations.

$13,595

Or lease for $269/mo. for 60 months *

Package includes:

- The Lombart CS-4 Chair & Stand
- Topcon VT-10 Refractor
- Topcon SL-2G Slit Lamp
- Reichert LongLife Chart Projector with mount, slide & screen
- Upgrade to the Lombart CVSi21 for only $2000 more or to the CVS-PC for only $1500 more — Additional upgrades & configurations available.

(1-800-566-2278)

Call 1-800-Lombart

Or Your Local Lombart Representative.

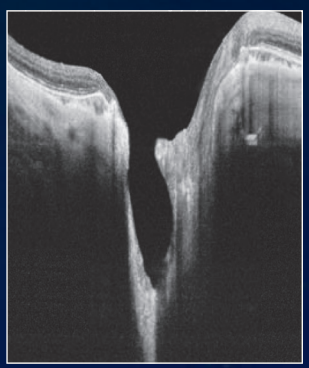
Corporate Office - 5358 Robin Hood Road, Norfolk, VA 23513-2430
757-853-8888 | FAX 757-855-1232 | 800-566-2278 | 800-446-8092
www.lombartinstrument.com

ATLANTA•BALTIMORE/WASHINGTON D.C.•BOSTON•BOYNTON BEACH/MIAMI•BRADENTON•CHARLOTTE
CHICAGO•CINCINNATI•DALLAS•DENVER•DETROIT•GREENSBORO•HOUSTON•KANSAS CITY•KNOXVILLE•LOS ANGELES
MILWAUKEE•MINNEAPOLIS•NEW JERSEY/NEW YORK•NORFOLK•PORTLAND•SACRAMENTO•SAN DIEGO•SAN FRANCISCO

***Lease rate subject to credit approval, 1st payment is paid for by leasing company at signing with 59 remaining rental payments of $269 and a $1.00 purchase option. Taxes, freight and installation additional. Hand Instruments optional. Quantities limited. Subject to change without notice.**

Save the Date!

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



Date: **Sunday, November 17th**

Time: 5:30 pm Registration, Cocktails & Hor d'oeuvres
6:00 pm Presentation

Venue: **W New Orleans**
Great Room
333 Poydras Street
New Orleans, LA 70130
Phone: 504-525-9444

Speaker	Affiliation	Presentation Title
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"*

3 Ways to Register!*
Online: www.revophth.com/OCTnov17
Call: 866-730-9256
Email: ReviewMeetings@Jobson.com

Sponsored by
TOPCON
CONNECTING VISIONS

Sponsored by
REVIEW of Ophthalmology

This event is not affiliated with the official program of the Joint Meeting.
Please refer to your state laws for any attendance restrictions. Attendance at this event is limited to eye care professionals. Due to individual state legislation, physicians from Minnesota, Vermont and Massachusetts may not attend this symposium.

*Registration is Complimentary

their visual deficit than those with less-severe disease. That awareness might explain why they were more likely to use their medications as directed.

Our second study looked for correlations between disease severity, medication use and compliance with follow-up visits.[3] After adjusting for confounding factors, the data revealed that being less adherent to the recommended follow-up schedule was associated with more severe glaucomatous disease (*See Table 2*). Patients who had only mild or moderate glaucoma were more compliant with keeping appointments as recommended than those with more severe disease. Given the cross-sectional nature of the study, we were unable to address the issue of causation—i.e., did more regular follow-up result in better outcomes? Nevertheless, the findings are a basis for exploring this hypothesis further in a prospective study.

Table 1. Multivariable Logistic Regression Analysis of Factors for Poor Medication Adherence in Glaucoma Patients (n=126)[1]

Variable	Adjusted Odds Ratio	P Value
Age (per year)	1.03 (0.99-1.07)	0.22
Gender	1.07 (0.50-2.29)	0.87
Race (Asian vs. non-Asian)	0.61 (0.27-1.39)	0.24
Education (less than high school vs. more)	0.77 (0.34-1.74)	0.53
Glaucoma diagnosis (POAG vs. other)	0.85 (0.40-1.81)	0.67
No. of medications (1 vs. ≥2)	0.66 (0.28-1.57)	0.35
Years of having glaucoma (per year)	1.00 (0.93-1.08)	0.92
Disease severity (mild/moderate vs. severe)	1.54 (1.03-2.31)	0.04

In contrast to a previous study, this data indicated that patients with more severe disease were more compliant with medication use, not less.

Making Sense of the Data

How can we account for the finding that patients who were more likely to use their medications as prescribed were less likely to return for follow-up visits? It's possible that these patients were thinking, "Well, I'm fine. I don't need to go see the doctor so often because if I'm taking my medications, the disease must be under control." In contrast, those who were not taking their medications regularly may have been more fearful of the adverse consequences of medication noncompliance and felt a greater need for regular surveillance.

Another question is whether the association between disease severity and follow-up inconsistency reflects some kind of causal link. If patients with worse disease are less reliable about returning for follow-up visits, is the worse condition of the eyes partially interfering with the patients' return? Or is the failure to return (due to some other cause) leading to a worsening of the disease?

Unfortunately, we can't fully answer that question in a cross-sectional study, and performing a prospective randomized trial to address the issue would require closer surveillance of one group of glaucoma subjects versus another with equally severe disease, a study design that may not be considered ethical.

Interestingly, we found no racial or ethnic correlations to the likelihood of returning for follow-up visits in the study. The only factors that correlated with poor follow-up were disease severity and glaucoma medication usage. In contrast, some previous studies of other cohort populations have found associations between factors such as race and ethnicity and inconsistent follow-up.[4] And, of course, some patient populations might face fewer practical obstacles to returning for follow-up visits than was the case with our population. There may also be differences in appreciating the need to return for checkups amongst different patient populations, so our results don't necessarily reflect the situation in every ophthalmology practice.

Nevertheless, the associations we found between medication usage, greater disease severity and poor follow-up compliance suggest that compliance with follow-up may be a complex and underappreciated parameter that influences the well-being of glaucoma patients. These data are a reminder: Using your medications properly is important, but it's not a substitute for appropriate recommended follow-up to maximize your chances of a good outcome.

Clinical Implications

Given this new data, clinicians may want to put more emphasis on conveying to their patients the importance of adherence to recommended follow-up. Using medications as prescribed is still important, but without timely, regular examinations to check the patient's status and adjust the medications as necessary—as well as offer non-medical therapeutic options when appropriate—patients may be at greater risk of vision loss.

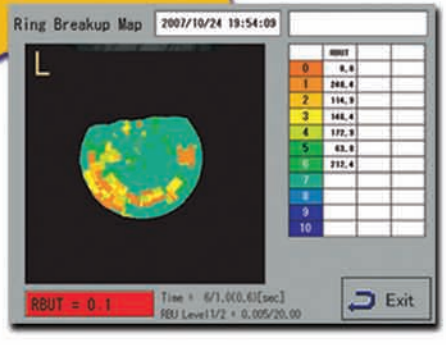
As noted, our studies did not find an association between ethnicity or race and follow-up compliance, but other studies have. So along with emphasizing the importance of follow-up, clinicians may want to make an extra effort to address the needs of specific patient groups to

TOMEY®

AUTOREFRACTOR/KERATOMETER/ TOPOGRAPHER

RT-7000 (3-in-1)

Dry Eye Software Included!



- 3 Functions in 1 Instrument: Auto Refractor, Keratometer, & Topographer
- Easy & Fast Touch Screen
- Auto Alignment/Shot
- Tear Stability Analysis System-Mode for Dry Eye
- Diameter Measurement of Cornea & Pupil

888-449-4045 • WWW.TOMEYUSA.COM

increase the likelihood of them returning in a timely manner. If your glaucoma patient population includes patients whose first language is not English, for example, you may consider providing information and instructions in multiple languages.

Studies have also found that poor follow-up compliance is associated with unfamiliarity with the necessary treatment duration, lack of knowledge about the permanency of glaucoma-induced vision loss and the perception that it isn't important to attend follow-up visits. Making sure your patients don't fall into any of these categories could go a long way toward changing their behavior, in terms of coming back for follow-up visits. Electronic health records may be able to help in this regard. Currently, some systems have the ability to print out an information sheet for each patient at checkout; it should be possible to have such a sheet available in multiple languages.

In an ideal world, one way to deal with poor follow-up compliance would be to treat the glaucoma in a manner that doesn't require frequent follow-up. Unfortunately, such an option doesn't currently exist. Laser trabeculoplasty is helpful in some situations in which people have difficulty returning for follow-up, perhaps in developing countries; but in general the pressure reduction achieved is moderate and the magnitude and length of the effect is variable, making appropriate follow-up a necessity. Surgery is an option we sometimes resort to in order to address an individual's poor compliance with using medication; but again, follow-up may be even more important in these situations. (Certainly when trabeculectomy is performed, follow-up is crucial.)

One possibility for getting patients to follow-up in a timely manner is to coordinate their care with the assistance of someone designated by the practice. This might also be another area in which electronic medical records could help. If a patient fails to return at the scheduled time, the system could contact the patient by phone or automated email, perhaps based on the patient's preference, while also alerting staff if the patient fails to reschedule.

Table 2. Multivariable Logistic Regression Analysis of Factors for Poor Follow-up Adherence in Glaucoma Patients (n=206)[3]

Variable	Adjusted Odds Ratio	P Value
Age (per year)	1.00 (0.96-1.03)	0.81
Gender	0.60 (0.32-1.12)	0.11
Race (Asian vs. non-Asian)	0.78 (0.41-1.47)	0.46
Education (more than high school vs. less)	1.10 (0.58-2.08)	0.68
Years of having glaucoma (per year)	1.03 (0.97-1.09)	0.36
Glaucoma surgery (yes or no)	0.73 (0.30-1.74)	0.39
Medications (yes or no)	3.29 (1.41-7.65)	0.01
Disease severity (severe vs. mild/moderate)	1.89 (1.21-2.94)	0.01
Expected no. of follow-up visits (mild: two visits; moderate/severe: three visits)	1.55 (0.60-3.98)	0.37

This study found that patients with severe disease were less likely to return for follow-up exams as recommended than those with less-severe disease.

Spreading the Word

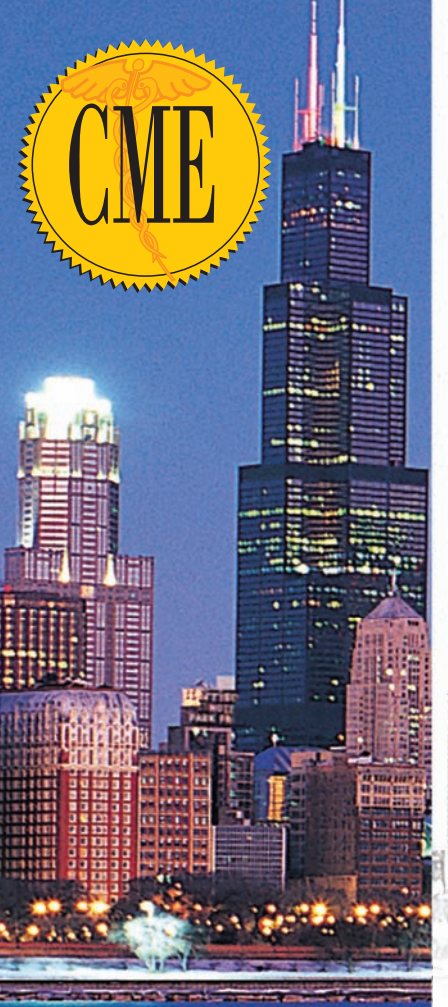
Unfortunately, among doctors treating glaucoma it's not uncommon to have the occasional patient come in having lost a significant amount of vision in one eye—a patient that we may have seen years ago who then dropped off the radar. At the outset, of course, glaucoma may not be associated with any symptomatology; patients may lose much of their vision before realizing that something is really wrong. At the same time, we all have a lot going on in our lives, so it's not hard to imagine how someone could postpone coming in for a checkup—especially if the patient doesn't fully grasp the seriousness of the situation. Sadly, by the time patients have lost vision from glaucoma, the effects are generally irreversible.

Either way, as the caregivers, it's our job to do everything possible to make sure our patients do understand the nature of the disease and the importance of returning for follow-up visits—especially in light of this new data. We have more available treatment options for glaucoma than ever before; keeping patients under appropriate surveillance, and thereby maximizing their likelihood of receiving the right treatment at the right time, may be the single most important factor in optimizing the odds of vision preservation.

That's a message worth spreading. REVIEW

Dr. Lin is a professor of clinical ophthalmology and director of the Glaucoma Service at the University of California at San Francisco. Dr. Singh is a professor of ophthalmology and director of the Glaucoma Service at Stanford University School of Medicine.

1. Ung C, Zhang E, Alfaro T, Murakami Y, Zhang M, Seider MI, Lin SC, Singh K. Glaucoma severity and medication adherence in a county hospital population. Ophthalmology 2013;120:6:1150-7.
2. Sleath B, Blalock S, Covert D, et al. The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. Ophthalmology 2011;118:2398-402.
3. Ung C, Murakami Y, Zhang E, Alfaro T, Zhang M, Seider MI, Singh K, Lin SC. The Association Between Compliance With Recommended Follow-up and Glaucomatous Disease Severity in a County Hospital Population. Am J Ophthalmol 2013;156:2:362-9.
4. Murakami Y, Lee BW, Duncan M, Kao A, Huang JY, Singh K, Lin SC. Racial and ethnic disparities in adherence to glaucoma follow-up visits in a county hospital population. Arch Ophthalmol 2011;129:7:872-8.



CME

SAVE THE DATE

Ophthalmic Symposium:

Prepare for 2014

December 7, 2013

Chicago, IL

Presented for

Ophthalmologists

Ophthalmologists in Training

Nurses

Technicians

This activity is designed as a comprehensive one-day course for ophthalmologists. A basic knowledge of anterior segment and refractive surgery are prerequisites for attendees.

PHYSICIANS
Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Institute for the Advancement of Human Behavior (IAHB) and *Review of Ophthalmology*®/ Jobson Medical Information LLC. The IAHB is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement
The IAHB designates this live activity for 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

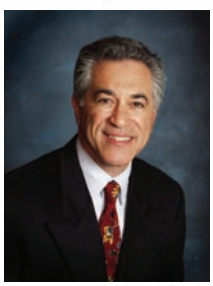
5 Ways to Register

Online: www.revophth.com/ChicOS2013

Phone: 866-627-0714 Email: ReviewLogistics@Jobson.com
Fax: 610-492-1039
MAIL: Review Group Meetings c/o Jobson
11 Campus Blvd., Ste. 100 Newtown Square, PA 19073

COURSE DIRECTORS

Stephen Lane, MD



Donald Serafano, MD

Jointly Sponsored by

REVIEW of Ophthalmology® IAHB

Partially supported by an independent medical educational grants from

Alcon® MST

The Dos and Don'ts of Phakic Lens Implants

These lenses can give excellent results in selected patients, but there's both an art and a science to their implantation.

Walter Bethke, Managing Editor

For patients who aren't ideal candidates for corneal refractive surgery, surgeons say it can be useful to have phakic lenses in your armamentarium. However, performing an intraocular procedure, especially with the crystalline lens still present, presents a number of challenges different from those associated with LASIK and PRK. Here, several experts adept at implanting these lenses tell how you can enjoy safer, better outcomes.

The Visian ICL

For the Staar Visian, surgeons say there are several stages of the lens measurement and implantation that are crucial.

• ***Preop measurements.*** "The endothelial cell count is important for both [the Visian and the Verisyse]," says Majid Moshirfar, MD, director of refractive surgery and cornea for the Moran Eye Center at the University of Utah. "So the surgeon needs a good anterior chamber depth measurement. With the Visian, it is still a challenge to get an exact measurement of the sulcus-to-sulcus diameter, which is a key to its implantation. With the advent of high-frequency ultrasound, we have a better idea of what that measurement is behind the iris, but, despite that, you can't control the amount of separation that will exist between the Visian and the anterior lens capsule, which should be a vault of between 250 and 500 µm. In some cases, you may find that the vault is good in the beginning but gradually decreases, or you may be surprised that the vault is a lot less than you anticipated. There are only four sizes of the Visian so, as a result, not every patient will fit perfectly into one of them, meaning you can't control the lens vault."

Dr. Moshirfar says there are a variety of ways to measure the sulcus-to-sulcus diameter, but he recommends ultrasound biomicroscopy if at all possible, and even has a certified ultrasonographer who does the measurement in each case to minimize variability. "If my patient's anterior chamber is very deep—from 3.6 to 4 mm—and if I have a good sulcus-to-sulcus measurement, the Visian is a good option," Dr. Moshirfar says. "But if I don't have a solid sulcus-to-sulcus measurement I think the Verisyse would be a good choice."

• ***Peripheral iridotomies.*** Dr. Moshirfar says that in some cases the Visian may float around a bit, making two preop iridotomies imperative. "With the Visian, you need to make your YAG PIs before the surgery, preferably one to three weeks prior," says Dr. Moshirfar. "You need to make two PIs and make them peripheral enough so patients don't have aberrations as a result of them, because in some cases patients can see the iridotomies as well as light distortions in the periphery, especially if they have large palpebral fissures and don't have the superior brow or lid covering the superior iris. It's very important that you put the PIs around the 10 o'clock or 11 o'clock positions, or at 1 o'clock and 2 o'clock. Try to avoid the 2:30, 3 o'clock, and 9 o'clock positions, which will cause patients to definitely see the PIs and the light coming through them. Sometimes, you even have to take the patient into the operating room and tattoo the cornea in those areas so they don't see the light coming through the PIs."

Minneapolis surgeon Sherman Reeves says that doing the PI ahead of time has a couple of benefits. "If I haven't obtained a UBM, I can do

This article has no commercial sponsorship.

CME

Go Further—Without Leaving Home

Continue your professional development and sharpen your clinical skills through convenient CME programs online and on your schedule.

Review of Ophthalmology® offers continuing education for physicians and staff, covering the latest in disease diagnosis and treatment, surgical advances and other topics, available any time on our website.

www.revophth.com/continuing_education/

Download a QR scanner app. Launch app and hold your mobile device over the code to view www.revophth.com/continuing_education/.

REVIEW® of Ophthalmology

it at that visit, too," he says. "Also, though it's uncommon, you can get some bleeding with an intraoperative surgical PI, so I like to keep the actual surgery as quiet as possible."

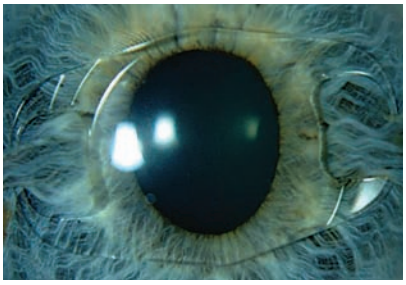
• ***Folding and implantation.*** Dr. Moshirfar recommends using OcuCoat in conjunction with the Visian. "Mix the OcuCoat 50/50 with saline solution in the lens cartridge," he says. "Make sure the lens is symmetrically folded and not torqued in the cartridge. And don't put too much OcuCoat into the anterior chamber—use just enough so you can put your lens inside and behind the iris. As the lens unfolds in the chamber, be patient and inject it slowly so the first set of wings of the ICL can gradually open. Then, slowly tuck them beneath the nasal iris. As the lens unfolds, you can get the other two ends of the ICL under the temporal iris. Making sure that the patient is well-dilated is very helpful.

"Later, when doing I/A, don't be overly aggressive," Dr. Moshirfar adds. "This can create turbulence in the anterior chamber that can create transient anterior subcapsular vacuoles, and can cause some swelling in the anterior lens capsule's epithelial cells, which could cause issues later."

The Verisyse

The AMO Verisyse goes into the anterior chamber, so surgeons say its considerations differ from the posterior chamber Visian.

• ***Anterior chamber depth.*** Unlike the Visian, which relies on the sulcus-to-sulcus measurement, the anterior chamber depth and its vault size for proper results, surgeons say that the Verisyse is mainly dependent on the anterior chamber depth. "The key is you have to have an anterior chamber depth of at least 3.2 mm," says Asim Piracha, MD, associate professor in ophthalmology and visual sciences at the University of Louisville. "A nice feature of the Pentacam HR is an Artisan/Verisyse preop calculation, that lets you make sure the eye has the normal anatomy for a Verisyse implant. The device shows a virtual image of the Verisyse in the patient's anterior chamber, demonstrating whether or not there's enough space for the lens. It will also show what the patient's chamber will look like in 20 or 30 years, since as we age the natural lens thickens and the chamber gets narrower."



Using a needle to enclavate the iris into the clips on either side of the Verisyse can be challenging, surgeons say.

• ***Incision.*** While the Visian is foldable and goes through a temporal clear cornea incision, the Verisyse requires a 5.5 to 6 mm incision that's not completely corneal: surgeons recommend limbal-corneal or scleral-limbal. Because the incision's large, many surgeons prefer making it superiorly. "Most of these high myopes who receive the Verisyse have with-the-rule astigmatism or oblique astigmatism, so it makes sense to make a superior wound," says Dr. Moshirfar. "That way, afterward when there is conjunctivalization of the cornea in that area, the vessels don't look so red and patients don't have the look of episcleral inflammation. The upper lid covers it up and it heals nicely." Surgeons also recommend a nerve block in Verisyse patients to avoid issues from squeezing.

Managing sutures is also a part of the Verisyse surgery. "I make a limbal incision, make a groove, then create a nice step in the groove," says Dr. Piracha. "I put one slipknot suture in the center of the wound after I put the lens in, which maintains the chamber so I can better work in it. This is important because these myopes often have floppy eyes and you worry about chamber collapse and the lens touching endothelium. I then perform enclavation *[discussed below]* and then pass the next two sutures and, before tying them, remove all the viscoelastic from the anterior chamber." For viscoelastic, Dr. Piracha recommends a cohesive visco that comes out easier than a dispersive. "I don't like a dispersive because it stays in the eye, is more difficult to remove and can cause pressure spikes."

• ***Enclavation.*** This is a maneuver unique to the Verisyse that fixates it in place on the iris. To do it, the surgeon uses a special needle to bunch up bits of iris into small clips on either end of the lens. "If I do a superior incision, I do my nasal enclavation first because there's less space on that side because the pupil tends to be more nasal, as well as superior," says Dr. Piracha. "Then I do the temporal enclavation because I have more space. If I'm using a temporal incision—in cases of against-the-rule astigmatism—I do the superior enclavation first."

Dr. Moshirfar says it pays to enclavate correctly the first time. "You really shouldn't try to enclavate each side more than twice," he says. "Even if the lens isn't perfectly centered, don't keep trying, because you'll reach a point where the iris is traumatized and you won't have enough iris for the enclavation. The best advice I can give is to mark the center of the pupil on the corneal surface and then place two tiny ink marks on the cornea corresponding to the spots on the iris where you will want to enclavate. This way, you can gauge your centration once you're in the eye because, by that time, the pupil may be a different shape." REVIEW

Merchandise Offered

Equipmentand Supplies

EquipmentandSu pplies

Practice For Sale

Professional Opportunities

Ophthalmology and Subspecialty Opportunities

Geisinger Health System (GHS) is seeking candidates to join the Department of Ophthalmology for the following positions:

- BC/BE fellowship-trained Surgical Retina physician for Geisinger Wyoming Valley (GWV) Medical Center, Wilkes-Barre, Pa.
- BC/BE Cornea/Refractive Surgery Ophthalmologist for Geisinger–Scenery Park, State College, Pa.

About the Surgical Retina Physician Position:

- Join a team consisting of a General Ophthalmologist, Glaucoma specialist and Optometrist
- Established patient base with an experienced support staff and photographer
- Unique technologies include a Fluorescein camera, OCT, HVF and laser
- Teaching opportunities exist with 6 residents
- Research opportunities available

About the Cornea/Refractive Surgery Ophthalmologist Position:

- Opportunity to start up a new practice and develop new programs
- Work with a surgical retina physician and a local Optometry practice
- Enjoy a strong referral base from Geisinger's community practice sites
- Candidate should possess exceptional surgical skills and a dedication to patient care

Discover for yourself why Geisinger has been nationally recognized as a visionary model of integrated healthcare.

For more information, please visit geisinger.org/careers or contact: Autum Ellis, Department of Professional Staffing, at 1-800-845-7112 or amellis1@geisinger.edu.

GEISINGER HEALTH SYSTEM

EYES OF THE SOUTHWEST
Eye Physicians & Surgeons

OPHTHALMOLOGIST

EYES OF THE SOUTHWEST is interested in hiring a partnership quality, personable, ethical, and skilled general, glaucoma or cornea trained Ophthalmologist for a busy practice in New Mexico. This newly expanded and renovated 6,500+ sq ft progressive practice currently has 2 Ophthalmologists, 9 lanes, 6 techs. Area demographics are very favorable with a large geographic referral base. The position offers a generous salary with incentive bonus and a wonderful growth potential in a beautiful Southern New Mexico setting. Hunting, Skiing, Hiking, and Fishing are all within a short drive. An international airport is 45 minutes away. This is an awesome place to raise a family. The candidate needs to be an outstanding cataract surgeon and an outstanding diagnostician. Formal subspecialty training in glaucoma or cornea a plus but not necessary. The candidate should expect to see 30+ patients a day and must have a good work ethic. Must be a personable, ethical, and skilled surgeon. Board certification or eligibility essential. Subspeciality skills welcomed.

Contact:
Edward V. Hernandez, MD
(575) 635-1739 or email:
ehernandez@eyesofthesouthwest.com

Rocky Mountain Eye Center is looking for a **Board Certified or Board eligible General Ophthalmologist** for a seven physician Ophthalmology practice in beautiful Western Montana. This position will be available in 2014 in our busy Butte satellite office. We also have a full time Optometrist at this location. The Rocky Mountain Eye Center has been serving Western Montana for more than 75 years. The main office is located in Missoula with an ophthalmic only surgery center onsite. We also have full time locations in Butte and Hamilton. Subspecialties include surgical retina, glaucoma, oculoplastics, cornea and pediatrics. There is also an optical shop and contact lens department in each location. Butte is an area rich in recreational opportunities with skiing, fishing, hunting, golf, kayaking, rafting and more all in your back yard.

www.rockymountaineye.com
Please contact for further information:
Dr. Roger Furlong at **rfurlong@rmeec.com**
or Darlene Timmerhoff, Administrator at
timmerhoff@rmeec.com

Do You Have Positions Available?

Contact us today for classified advertising:
Toll free: **888-498-1460**
E-mail: **sales@kerhgroup.com**

REVIEW of Ophthalmology

Products and Services

P.M. MEDICAL BILLING AND CONSULTING

SPECIALIZING IN OPHTHALMOLOGY BILLING & CONSULTING

- *National, full service billing to ophthalmologists*
- *Maximum reimbursement is guaranteed*
- *Staff consists of Ophthalmic techs, expert coders & billers*
- *Increased revenue/low denial rate/complete & unrelenting follow up*

We specialize in old, outstanding AR, Practice Management & Credentialing

Contact us at:
pmmedbill@aol.com
or call us toll-free at:
1-888-PM-BILLING
for a free in-office consultation
WWW.PMOPHTHALMOLOGYBILLING.COM

REVIEW of Ophthalmology

CONTACT US TODAY
FOR CLASSIFIED ADVERTISING
Toll free: **888-498-1460**
E-mail: **sales@kerhgroup.com**

A contact lens wearer develops a corneal ulcer that is nonresponsive to multiple therapies.

Margaret Greven, MD

Presentation

A 55-year-old man with a history of soft contact lens wear presented to the Wills Eye Cornea Service for evaluation of six weeks of pain and blurry vision in the right eye. The patient initially presented to an outside optometrist who diagnosed a corneal abrasion in the right eye. Two weeks later he presented to an outside ophthalmologist with worsening symptoms in his right eye, was diagnosed with a corneal ulcer, and was initiated on moxifloxacin 0.5% four times per day. He continued to worsen, and three days later he was started on fortified vancomycin drops every hour while awake, oral valacyclovir 500 mg three times per day, and topical trifluridine nine times per day, and corneal cultures were obtained. Cultures were negative for bacteria and fungi. Three weeks later the patient presented to the Wills Eye Cornea Service due to persistence of his symptoms. Prior to presenting to Wills, the patient had at one time been on the following treatments: loteprednol 0.5%; moxifloxacin 0.5%; fortified vancomycin; trifluridine; tobramycin/dexamethasone; valacyclovir; doxycycline; and artificial tears.

Medical History

At his initial visit to Wills Eye, the patient denied contact lens overwear, sleeping in lenses, showering or swimming in lenses. His ocular history was otherwise negative. His past medical history was significant only for hyperlipidemia. His only systemic medication was a statin.

Examination

The patient's visual acuity with correction was 20/100 in the right eye and 20/20 in the left eye. His pupils were equal and reactive with no afferent pupillary defect. His motility was full, and intraocular pressures were 8 mmHg bilaterally.

On slit-lamp examination, the right eye revealed 1+ injection and a 3.75 mm x 4 mm infiltrate with an overlying epithelial defect *(See Figure 1)*. The left eye had trace injection, scattered peripheral subepithelial corneal infiltrates, and a pseudo-dendritic epithelial staining pattern *(See Figures 2 & 3)*.

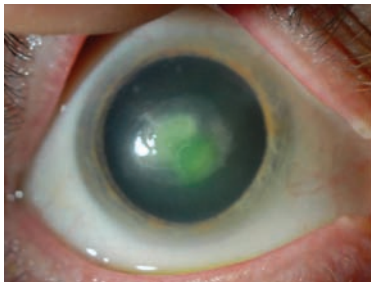


Figure 1. Slit-lamp photo of the right eye on presentation showing central infiltrate with overlying epithelial defect.

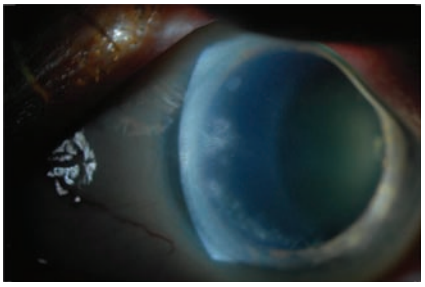


Figure 2. Slit-lamp photo of the left eye on presentation with peripheral subepithelial infiltrates.

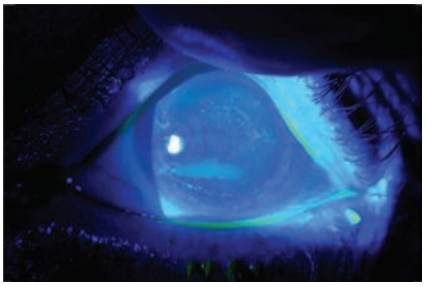


Figure 3. Slit-lamp photo of the left eye on presentation with pseudo-dendritic staining pattern.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 80

Before reading on, please see p. 79 for presenting complaint, history and examination.

Diagnosis, Workup and Treatment

After examination of the right eye the patient was thought to have a bacterial ulcer with a component of medicamentosa from his multiple topical treatments. However, once the pseudo-dendritic staining and subepithelial infiltrates were noted in the asymptomatic left eye, suspicion was raised for *Acanthamoeba* keratitis. Both eyes were re-cultured for bacteria and fungi, corneal scrapings from both eyes were sent for pathology, and the patient's contact lens case was sent for cultures. Polymyxin/bacitracin ophthalmic ointment every two hours was started in the right eye. Two days later pathology results were reported positive for *Acanthamoeba* in both eyes *(See Figure 4)*. Corneal cultures and contact lens case cultures were negative. The patient was started on dual therapy with polyhexamethylene biguanide (PHMB) and propamidine (Brolene) drops every hour around the clock in both eyes.

The patient had a slow improvement on this treatment regimen *(See Figures 5 & 6)*. The medications were gradually tapered and the patient received a five-month course of treatment in the right eye and a four-month course of treatment in the left eye. Visual acuity in the right eye after treatment remained 20/200 due to central corneal scarring, while in the left eye, visual acuity after treatment was 20/20.

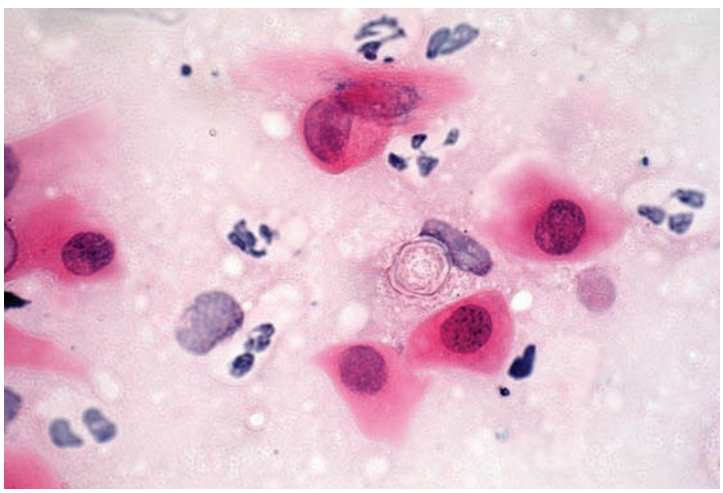


Figure 4. *Acanthamoeba* cysts seen in corneal scrapings from both eyes.

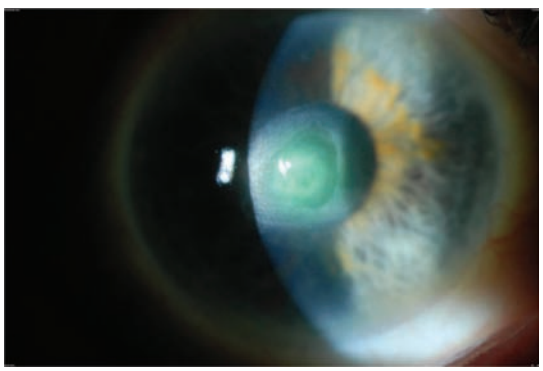


Figure 5. Slit-lamp photo of the right eye improving after two months of treatment; vision 20/200.

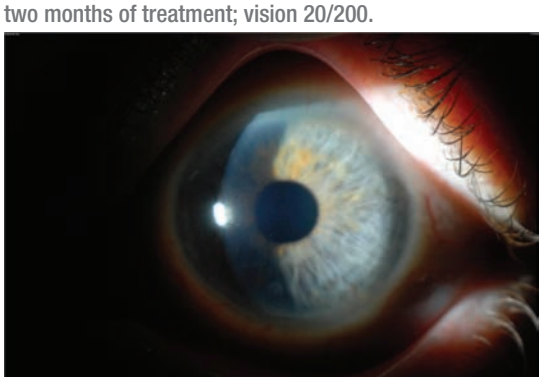


Figure 6. Slit-lamp photo of the left eye after two months of treatment; vision 20/20, subepithelial infiltrates and pseudo-dendritic staining resolved.

Discussion

Acanthamoeba keratitis is an infection of the cornea caused by cyst-forming protozoans ubiquitous in the environment.[1] The condition was first described in the early 1970s but an increase in incidence occurred in the 1980s associated with an increase in soft contact lens wear.[2] The most well-known and strongest risk factor for *Acanthamoeba* keratitis is contact lens wear, as well as inadequate lens disinfection.[1-3] Additional risk factors in contact lens wearers include swimming in lenses, overnight wear of lenses and exposure of lenses to contaminated water and well water.[4] Other risk factors that disrupt the normal epithelial barrier of the cornea include minor corneal trauma and epithelial basement membrane dystrophy; dry eye may also predispose to disease.[1-3]

Acanthamoeba keratitis is often initially misdiagnosed as herpetic or bacterial disease, leading to delay in

initiation of appropriate treatment.[4,5] Clinical features of *Acanthamoeba* keratitis include pain out of proportion to clinical signs, photophobia and tearing.[1] Absence of pain does not, however, preclude the diagnosis. Early in the course of the disease, a pseudodendritic epitheliopathy, subepithelial infiltrates and radial keratoneuritis may be noted.[1,4] Our patient in this case demonstrated the early *Acanthamoeba* keratitis paradigm in his asymptomatic left eye. Of note, although this eye was clearly involved, the patient was without pain in his left eye. Later disease is characterized by ring infiltrates, ulceration, keratic precipitates and sometimes hypopyon formation, demonstrated by our patient's symptomatic right eye.[1,4] Prompt diagnosis and treatment initiation is important in *Acanthamoeba* keratitis because early treatment leads to better visual outcomes.[4,5]

Definitive diagnosis of *Acanthamoeba* keratitis can be made only with cultures or histology of corneal scrapings as in our case.[2] Confocal microscopy is used in some centers to aid in diagnosis, with reported sensitivity in one study of 90.6 percent and specificity of 100 percent.[6] If clinical suspicion for *Acanthamoeba* keratitis warrants, however, treatment should not be delayed pending definitive diagnosis.

Treatment of *Acanthamoeba* keratitis is aimed at killing the cystic, or dormant, form of the organism, which is highly resistant to most treatments and can persist for months to years.[1,2] Two classes of medication have activity against *Acanthamoeba* cysts: biguanides and diamidines. These medications are not commercially available in the United States and can only be obtained from compounding pharmacies or from overseas. The two biguanides currently in use are polyhexamethylene biguanide (PHMB) 0.02% and chlorhexidine 0.02%. These agents act by disrupting the cytoplasmic membrane of *Acanthamoeba* trophozoites and cysts resulting in cell death.[1] The diamidines include propamidine (Brolene) 0.1% and hexamidine 0.1% and also work through increasing membrane permeability in both trophozoites and cysts.[1] Treatment may be initiated with either a biguanide alone or a biguanide in addition to a diamidine and is typically prescribed every hour around the clock for the first few days of treatment. Practice patterns vary by provider as there are no studies demonstrating efficacy of dual therapy over monotherapy.[7] Our patient was initially started on dual therapy with PHMB and propamidine but due to propamidine toxicity finished out his course on PHMB alone. His overall course of five months in one eye and four months in the other eye is typical, as most patients require several months of treatment prior to resolution.[2]

Acanthamoeba keratitis is a challenging disease to diagnose and to treat. As early diagnosis and treatment portends a better visual prognosis, *Acanthamoeba* must be considered in any patient thought to have herpetic epithelial disease, contact lens-related subepithelial infiltrates or a corneal ulcer unresponsive to treatment. REVIEW

The author would like to thank Christopher Rapuano, MD, and Ralph Eagle Jr., MD, for their assistance in preparing this case.

1. Dart JK, Saw VP, Kilvington S. Acanthamoeba keratitis: Diagnosis and treatment update 2009. Am J Ophthalmol 2009;148:487-499.
2. Hammersmith KM. Diagnosis and management of Acanthamoeba keratitis. Curr Opin Ophthalmol 2006 Aug; 17(4): 327-31.
3. Page MA, Mathers WD. Acanthamoeba keratitis: A 12-year experience covering a wide spectrum of presentations, diagnoses, and outcomes. J Ophthalmol. 2013 Published online 2013 Jun 12.
4. Thebpatiphat N, Hammersmith KM, Rocha FN, Rapuano CJ, Ayres BD, Laibson PR, Eagle RC Jr., Cohen EJ. Acanthamoeba Keratitis: A Parasite on the Rise. Cornea 2007;26:701-706.
5. Chew HF, Yildiz EH, Hammersmith KM, Eagle RC Jr, Rapuano CJ, Laibson PR, Ayres BD, Jin YP, Cohen EJ. Clinical Outcomes and Prognostic Factors Associated With Acanthamoeba Keratitis. Cornea 2011;30:435-441.
6. Tu EY, Joslin CE, Sugar J et al. The relative value of confocal microscopy compared to superficial corneal scrapings in the diagnosis of acanthamoeba keratitis. Cornea 2008;27:764-767.
7. Oldenburg CE, Acharya NR, Tu EY, et al. Practice patterns and opinions in the treatment of acanthamoeba keratitis. Cornea 2011;30:1363-8.

(continued from page 60)

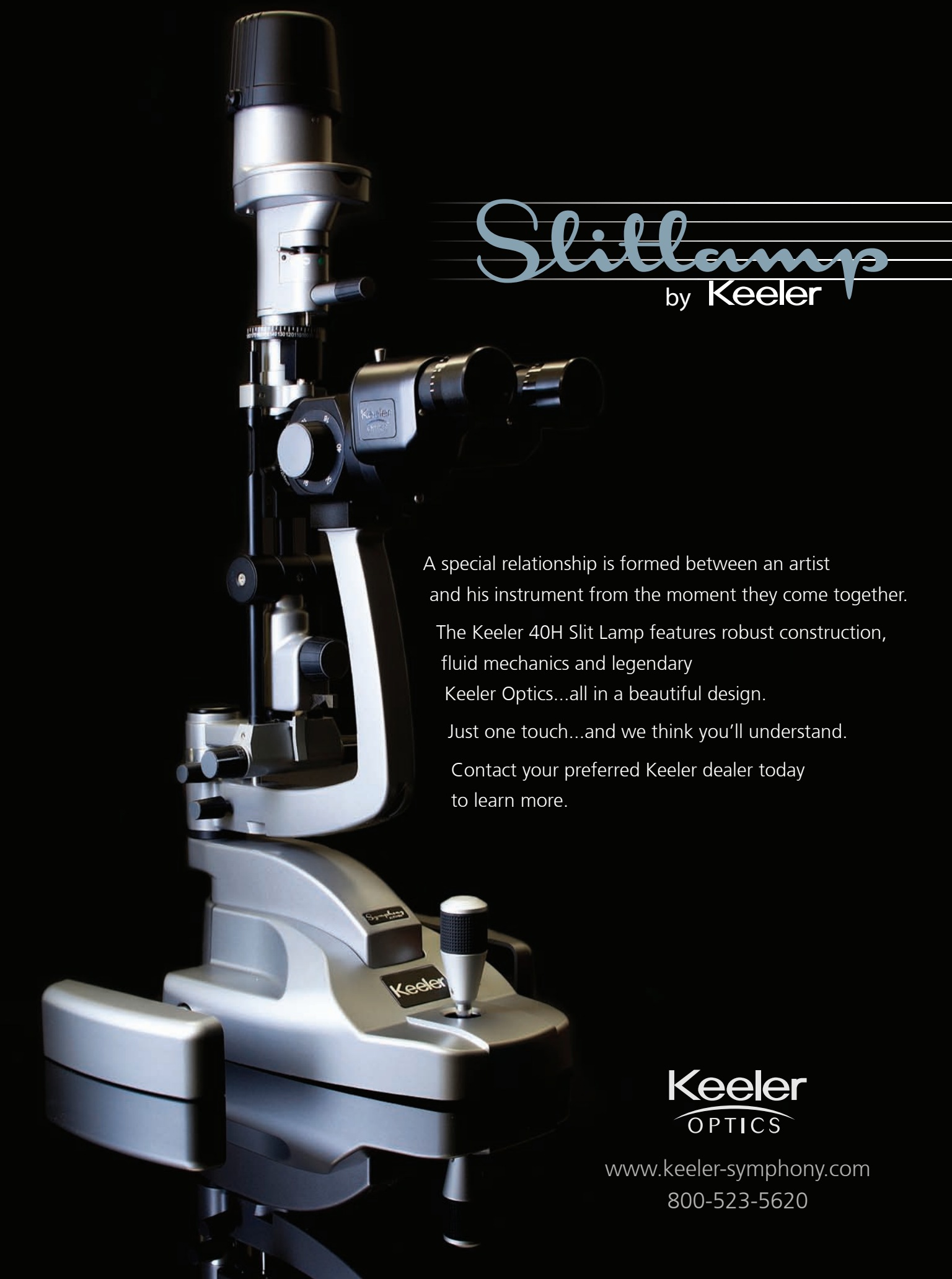
with inherited retinal degenerations potentially amenable to treatment with this technology, the future is brighter than it was before. REVIEW

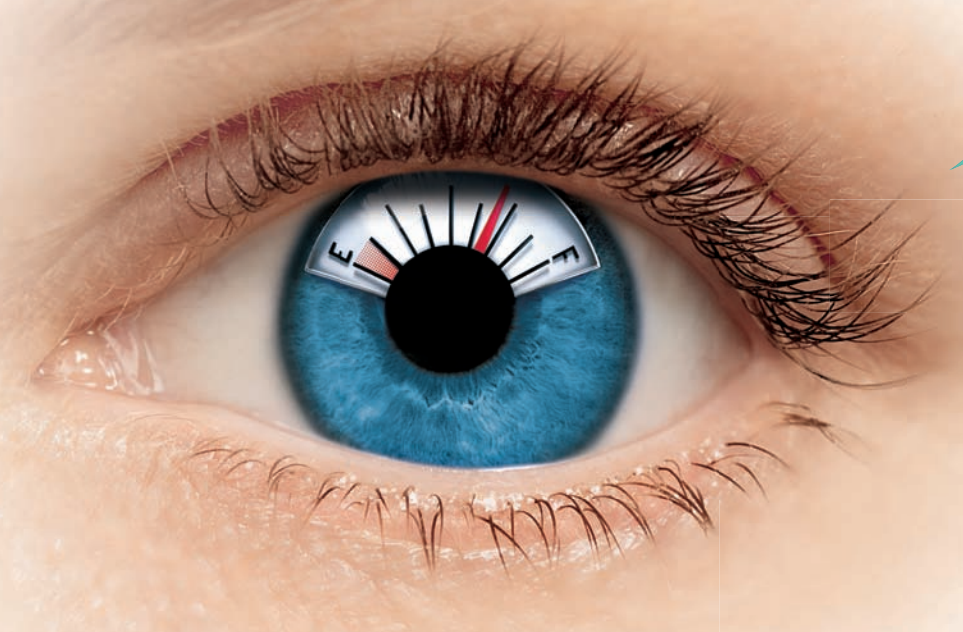
Dr. Campbell is a vitreoretinal fellow at the Casey Eye Institute, Oregon Health & Science University. Following fellowship, he will return to the Wilmer Eye Institute to serve as the Stephen J. Ryan Assistant Chief of Service. Dr. Stout is vice-president and a professor of ophthalmology at OHSU. Contact Dr. Stout at stoutt@ohsu.edu.

1. Friedmann T. A brief history of gene therapy. Nature Genetics 1992;2(2):93-98. doi:10.1038/ng1092-93.
2. Liu MM, Tuo J, Chan C-C. Gene therapy for ocular diseases. Br J Ophthalmol 2011;95(5):604-612. doi:10.1136/bjo.2009.174912.
3. Chung DC, Lee V, Maguire AM. Recent advances in ocular gene therapy. Curr Opin Ophthalmol 2009;20(5):377-381. doi:10.1097/ICU.0b013e32832f802a.
4. Maguire AM, Simonelli F, Pierce EA, et al. Safety and Efficacy of Gene Transfer for Leber's Congenital Amaurosis. N Engl J Med 2008;358(21):2240-2248. doi:10.1056/NEJMoa0802315.
5. Bainbridge JWB, Smith AJ, Barker SS, et al. Effect of Gene Therapy on Visual Function in Leber's Congenital Amaurosis. N Engl J Med 2008;358(21):2231-2239. doi:10.1056/NEJMoa0802268.
6. Cideciyan AV, Aleman TS, Boye SL, et al. Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics. Proc Natl Acad Sci USA 2008 Sep 30;105(39):15112-7. doi: 10.1073/pnas.0807027105. Epub 2008 Sep 22.
7. McClements ME, Maclaren RE. Gene therapy for retinal disease. Transl Res 2013. doi:10.1016/j.trsl.2012.12.007.
8. Maguire AM, High KA, Auricchio A, et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: A phase 1 dose-escalation trial. Lancet 2009;374(9701):1597-1605. doi:10.1016/S0140-6736(09)61836-5.
9. Mullard A. Gene therapies advance towards finish line. Nat Rev Drug Discov 2011 Sep 30;10(10):719-20. doi: 10.1038/nrd3572.
10. Cideciyan AV, Jacobson SG, Beltran WA, et al. Human retinal gene therapy for Leber congenital amaurosis shows advancing retinal degeneration despite enduring visual improvement. Proc Natl Acad Sci USA 2013;110(6):E517-25. doi:10.1073/pnas.1218933110.
11. Cepko C, Vandenberghe LH. Retinal Gene Therapy Coming of Age. Hum Gene Ther 2013. doi:10.1089/hum.2013.050.
12. Campochiaro PA. Gene Transfer for Neovascular Age-Related Macular Degeneration. Hum Gene Ther 2011;22(5):523-529. doi:10.1089/hum.2011.050.
13. Kauper K, McGovern C, Sherman S, et al. Two-year intraocular delivery of ciliary neurotrophic factor by encapsulated cell technology implants in patients with chronic retinal degenerative diseases. Invest Ophthalmol Vis Sci 2012;53(12):7484-7491. doi:10.1167/iovs.12-9970.
14. Campochiaro PA, Nguyen QD, Shah SM, et al. Adenoviral vector-delivered pigment epithelium-derived factor for neovascular age-related macular degeneration: results of a phase I clinical trial. Hum Gene Ther 2006;17(2):167-176. doi:10.1089/hum.2006.17.167.
15. Safety and Tolerability Study of AAV2-sFLT01 in Patients With Neovascular Age-Related Macular Degeneration (AMD)–Full Text View–ClinicalTrials.gov. clinicaltrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT01024998. Accessed January 18, 2013.
16. Singh MS, Charbel Issa P, Butler R, et al. Reversal of end-stage retinal degeneration and restoration of visual function by photoreceptor transplantation. Proc Natl Acad Sci USA 2013;110(3):1101-1106. doi:10.1073/pnas.1119416110.

REVIEW Advertising Index

This advertiser index is published as a convenience and not as part of the advertising contract. Every care will be taken to index correctly. No allowance will be made for errors due to spelling, incorrect page number, or failure to insert.


Slitlamp
by Keeler
A special relationship is formed between an artist
and his instrument from the moment they come together.
The Keeler 40H Slit Lamp features robust construction,
fluid mechanics and legendary
Keeler Optics...all in a beautiful design.
Just one touch...and we think you'll understand.
Contact your preferred Keeler dealer today
to learn more.
Keeler
OPTICS
www.keeler-symphony.com
800-523-5620



Restasis®
(Cyclosporine Ophthalmic Emulsion) 0.05%

restasisprofessional.com

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

For local co-pays, scan QR-code or visit restasiscopay.com

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.

ALLERGAN