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March 2015

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CATARACT ISSUE

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REVIEW NEWS
Volume XXII • No. 3 • March 2015

Kellogg Center Study Finds Generics Improve Adherence

When patients with glaucoma switched from a brand name drug to its generic counterpart, they were more likely to take their medication as directed compared to those who remained on the brand name drug, according to a study published online in *Ophthalmology*. Researchers at the University of Michigan Kellogg Eye Center and College of Pharmacy studied medication adherence rates 18 months before and after the first generic prostaglandin analogue glaucoma drug became available in March 2011.

Despite the potentially dire consequences for non-adherence, many patients struggle with their drug regimens. Along with known barriers—eye drops can be difficult to use, medication regimens may be complicated, and patients may not understand the consequences of poor adherence—the high cost of copays for brand name drugs is also a deterrent, the study suggests. "Some of my patients take as many as three or four different classes of these medications, and a number end up paying as much as $100 out-of-pocket every month for their medication," says Joshua D. Stein, MD, MS, glaucoma specialist and health services researcher at the U-M Kellogg Eye Center.

The report drew on a nationwide health-care claims database to study 8,427 patients with open-angle glaucoma who were 40 years and older and were taking PGAs, one of the most commonly prescribed class of drugs for glaucoma. All patients in the study had health insurance.

Dr. Stein and colleagues found that patients who remained on brand name drugs were 39-percent more likely to experience a decline in adherence compared to those who switched to the newly available generic drug latanoprost. The researchers cited several factors associated with improved adherence rates, among them, the use of the generic drug once it became available and lower copays after the generic drug became available.

The Michigan researchers found that black patients had decreased adherence compared to white patients, a concern because blacks tend to have more severe disease and often require a more complex medication regimen. However, a subset of blacks—those who switched to the generic drug—had a substantial improvement in adherence compared to blacks who remained on brand name products.

Dr. Stein observed that a sizeable group of patients—612 individuals or 7.3 percent of the study group—simply discontinued use of treatment altogether at the time the generic drug became available. While it was not clear why this occurred, the researchers urge that clinicians be alert for patients who stop taking their medicine, which can cause worsening of the disease and the need for costly surgical or medical treatment in the future.

"If clinicians suspect that a patient is struggling with medication adherence, it may be a good idea to switch from a brand name to a generic drug," advises Dr. Stein. He also encourages patients to ask their doctors if a generic alternative is available and appropriate for their circumstances.

Ranibizumab Restores Diabetic Vision Loss

Ranibizumab, commonly used to treat age-related vision loss, also reverses vision loss caused by diabetes among Hispanic and non-Hispanic whites, according to a new study led by investigators from the University of Southern California Eye Institute.

Diabetic retinopathy and diabetic macular edema are the leading causes of vision loss in working-age adults in the United States, according to the National Eye Institute. Laser surgery is the standard treatment for advanced stages of the disease, but previous research has shown that only 30 percent of patients saw improvement in their vision.

"We found that ranibizumab can save the sight of thousands of working-age individuals suffering from diabetic eye disease, as standard treatments such as laser are not as effective," said Rohit Varma, MD, MPH, director of the USC Eye Institute, professor and chair of ophthalmology at the Keck School of Medicine of USC and the study's lead author.

Dr. Varma's team developed a population-based model that suggests that administering 0.3 milligrams of ranibizumab (Lucentis) every four weeks to patients with diabetic macular edema would reduce the number of cases of vision impairment by 45 percent, or 5,134 individuals, and the number of cases of legal blindness by 75 percent, or 1,275 individuals. The model was based on the approximately 37,000 Hispanic and non-Hispanic white adults with diabetic macular edema in the United States for whom ranibizumab treatment could be used. Because other race and ethnic groups were not included in the study, the authors contend that the treatment may benefit even more people than their results show.

Could Laser Cure AMD?

A new technique reported in the February issue of the *FASEB Journal* suggests that during early stages, it might be possible to reverse age-related macular degeneration, a leading cause of blindness that is currently irreversible. The treatment involving a nanosecond laser may also have further implications for other eye diseases such as diabetic macular edema, diabetic retinopathy and retinopathy of prematurity.

"It is hoped that this study will provide a basis for the clinical use of the low energy nanosecond laser in those with early stage age-related macular degeneration and that such a treatment will limit the progression of the disease to the advanced, sight-threatening forms," said Erica L. Fletcher, OD, PhD, FAAO, a researcher involved in the work from the Department of Anatomy and Neuroscience at the University of Melbourne in Victoria, Australia.

To make their discovery, Dr. Fletcher and colleagues treated a group of

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REVIEW News

individuals with intermediate AMD in one eye with a single session of nanosecond laser treatment. These individuals underwent eye examinations every six months, out to two years post-treatment and the results were compared to an untreated group with early AMD. Anatomical examination of human and mouse eyes was used to determine the effect of the laser on the sensitive light-detecting retina.

In order to determine how this laser may help in limiting AMD, a mouse with a genetic mutation that predisposes it to developing one of the hallmark signs of AMD was treated with the nanosecond laser and structural and gene analysis was performed. Results showed that treating those with early AMD with this new low-energy nanosecond laser may limit disease progression. Importantly, unlike other lasers currently used to treat eye disease, the nanosecond laser does not result in damage to the sensitive retina. This study also showed evidence that nanosecond laser treatment in one eye can also produce positive effects in the other untreated eye. This raises the possibility that monocular treatment may be sufficient to treat disease in both eyes.

"This truly remarkable research is worth watching," said Gerald Weissmann, MD, editor in chief of the *FASEB Journal*, "because it may help usher in an era in which age-related macular degeneration is either eliminated or no longer considered a serious disease." The *FASEB Journal* is published by the Federation of the American Societies for Experimental Biology.

AMD Drug Choice Goes Beyond Price

Two drugs that treat macular degeneration are practically interchangeable—except for the price.

Ranibizumab costs up to $2,000 per dose, while bevacizumab is $50 per dose. Researchers at the Stanford University School of Medicine suspected that doctors treating Medicare patients would have a financial incentive to prescribe a more costly drug. So they would be more likely to prescribe ranibizumab than doctors in the Veterans Health Administration, who do not have that incentive.

As it turns out, the prescription practices for these two drugs aren't that straightforward, the researchers wrote in a Feb. 2 paper in *Health Affairs*.

"It's complicated," said senior author Kate Bundorf, MBA, MPH, PhD, associate professor of health research and policy. "The incentives facing physicians don't seem to be the only story."

Researchers examined data from both systems from 2005 to 2011. In 2011, Medicare physicians prescribed the less costly bevacizumab (Avastin) 63 percent of the time. Ranibizumab (Lucentis) was prescribed 37 percent of the time. If all of those injections had been reimbursed at the rate for bevacizumab, Medicare would have saved approximately $1.1 billion, according to a 2011 report by the Office of Inspector General in the Department of Health and Human Services.

In the VA system, ranibizumab was prescribed 52 percent of the time in 2011. Interestingly, however, prescription decisions at the VA varied regionally, with some centers prescribing primarily bevacizumab, others primarily ranibizumab, and others alternating between the two drugs.

Dr. Bundorf said she suspects that patients' financial incentives may also be influencing prescribing decisions; that is, they may be asking for the less-expensive drug, particularly if they're covered by Medicare, whose patient co-pays sometimes reflect the cost of the drugs. Some physicians may also be thinking of the system-wide effects when selecting the less expensive drug, she said.

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tive at treating macular degeneration. Bevacizumab was originally developed to treat cancer; ranibizumab was designed specifically for eye conditions.

Dr. Bundorf said the study illustrates the need for improvement in both health-care systems; for example, physicians could be offered incentives to select the best drug for the condition and save money.

Eye/Brain Link Sought to Treat Disparate Diseases

Researchers at LSU Health New Orleans have discovered gene interactions that determine whether cells live or die in such conditions as age-related macular degeneration and ischemic stroke. These common molecular mechanisms in vision and brain integrity can prevent blindness and also promote recovery from a stroke. The paper was published online in *Cell Death & Differentiation*.

"Studying the eye and the brain might hold the key to creating therapeutic solutions for blindness, stroke and other seemingly unrelated conditions associated with the central nervous system," says Nicolas Bazan, MD, PhD, Boyd Professor, Ernest C. and Yvette C. Villere Chair of Retinal Degeneration Research, and director of the Neuroscience Center of Excellence at LSU Health New Orleans. "The eye is a window to the brain."

Dr. Bazan and his research team discovered Neuroprotectin D1, which is made from the essential fatty acid, docosahexaenoic acid. Previous work showed that while it protected cells, the molecular principles underlying this protection were not known.

"During the last few years, my laboratory has been immersed in studying gene regulation," Dr. Bazan says. "We have uncovered a novel control that makes definitive decisions about whether a retina or brain cell will survive or die when threatened with disease onset. The gene mechanism that we discovered is the interplay of two genes turned on by the messenger Neuroprotectin D1."

The research team worked with human retinal pigment epithelial cells and an experimental model of ischemic stroke. They discovered novel mechanisms in cells with the ability to activate pathways that crosstalk one to another and then assemble consolidated responses that decide cell fate. The researchers found that the powerful messenger, NPD1, is produced on-demand in the brain and retina and that it elicits a network of positive signals essential for the well-being of vision and cognition. They showed that NDP1 bioactivity governs key gene interactions decisive in cell survival when threatened by disease or injury. They demonstrated that not only does NPD1 protect photoreceptors, but it also promotes remarkable neurological recovery from the most frequent form of stroke in humans.

How RGCs Alter Structure Holds Clue to Glaucoma

To better understand the cellular changes in retinal ganglion cells and how they influence the progression and severity of glaucoma, researchers at the University of California, San Diego, School of Medicine and Shiley Eye Institute turned to a mouse model of the disease. Their study, published Feb. 10 in *Journal of Neuroscience*, reveals how some types of retinal ganglion cells alter their structures within seven days of elevated eye pressure, while others do not.

"Understanding the timing and pattern of cellular changes leading to retinal ganglion cell death in glaucoma should facilitate the development of tools to detect and slow or stop those cellular changes, and ultimately preserve vision," said Andrew D. Huberman, PhD, assistant professor of neurosciences, neurobiology and ophthalmology. Dr. Huberman co-authored the study with Rana N. El-Danaf, PhD, a postdoctoral researcher in his lab.

Retinal ganglion cells are specialized neurons that send visual information from the retina to the brain. Increased pressure within the eye can contribute to retinal ganglion cell damage, leading to glaucoma. Even with pressure-lowering drugs, these cells eventually die, leading to vision loss.

In this study, Drs. Huberman and El-Danaf used a mouse model engineered to express a green fluorescent protein in specific retinal ganglion cells subtypes. This tool allowed them to examine four subtypes of retinal ganglion cells. The different cell types differ by the location in the eye to which they send the majority of their dendrites (cellular branches). Within seven days of elevated eye pressure, all retinal ganglion cells that send most or all of their dendrites to a region of the eye known as the OFF sublamina underwent significant rearrangements, such as reductions in number and length of dendritic branches. Retinal ganglion cells with connections in the ON part of the retina did not.

"We are very excited about this discovery," Dr. Huberman said. "One of the major challenges to the detection and treatment of glaucoma is that you have to lose a lot of cells or eye pressure has to go way up before you know you have the disease. These results tell us we should design visual field tests that specifically probe the function of certain retinal cells. In collaboration with the other researcher members of the Glaucoma Research Foundation Catalyst for a Cure, we are doing just that and we are confident these results will positively impact human patients in the near future." REVIEW

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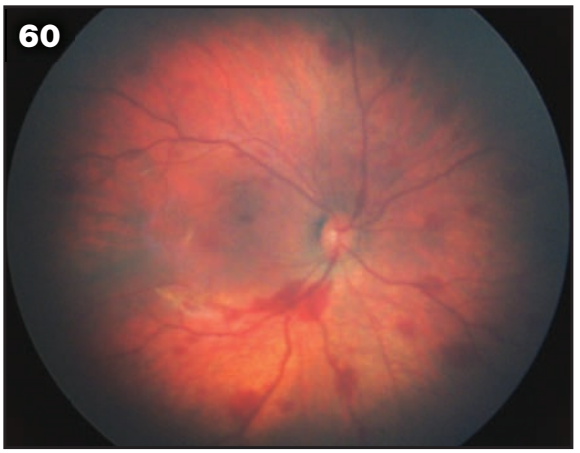

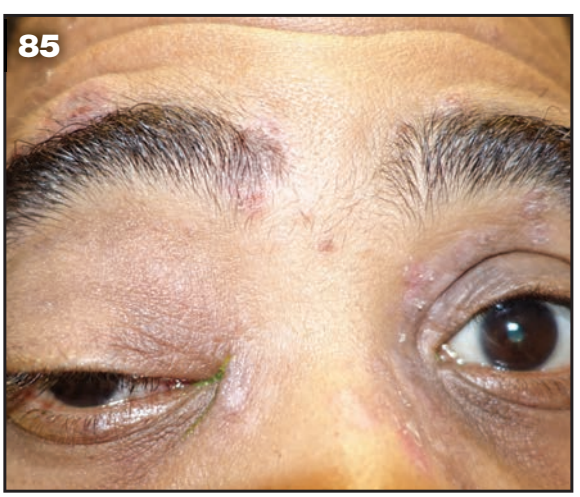

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IMPORTANT SAFETY INFORMATION – TECNIS® MULTIFOCAL 1-PIECE IOLs

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

INDICATIONS: TECNIS® Multifocal 1-Piece IOLs are indicated for primary implantation for the visual correction of aphakia in adult patients with and without presbyopia in whom a cataractous lens has been removed by phacoemulsification and who desire near, intermediate, and distance vision with increased spectacle independence. The intraocular lenses are intended to be placed in the capsular bag.

WARNINGS AND PRECAUTIONS: Inform patients of possible contrast sensitivity reduction and increases in visual disturbances that may affect their ability to drive at night or in poor visibility conditions. The lenses are intended for placement in the capsular bag and should not be placed in the sulcus. Weigh the potential risk/benefit ratio for patients with conditions that could be exacerbated or may interfere with diagnosis or treatment. Secondary glaucoma has been reported occasionally in patients with controlled glaucoma who received lens implants. Multifocal IOL implants may be inadvisable in patients where central visual field reduction may not be tolerated, such as macular degeneration, retinal pigment epithelium changes, and glaucoma.

ATTENTION: Reference the Directions for Use for a complete listing of Important Indications, Warnings, Precautions, and Adverse Events.

Abbott


Genetic Testing: New Resources & Challenges

New tests are expanding the usefulness of genetic analysis and promising to simplify the diagnostic process.

Christopher Kent, Senior Editor

If you're looking for an example of the rapid evolution of science, look no further than the field of genetics. Knowledge in this area is exploding, and that is translating into a steady increase in the use of genetic testing in the diagnosis and management of disease. Here, experts in this field discuss two major new developments that will impact ophthalmology; provide a look at some of the current resources available to physicians; and offer advice on how to make the most of these tools.

Two New Tests

Researchers at the Ocular Genomics Institute (associated with the Massachusetts Eye and Ear Infirmary and Harvard Medical School in Boston) have developed a CLIA-certified, next-generation, gene-sequencing protocol designed for patients with inherited eye diseases, including glaucoma, retinal degenerations and optic atrophy. The tests are referred to as Genetic Eye Disease panels, or GEDi. The GEDi-R test looks for mutations relating to retinal disorders; the GEDi-O test checks for mutations relating to optic atrophy and early onset glaucoma.

Clinical testing results, reported in a recent publication,[1] have demonstrated that the GEDi tests' ability to detect a single nucleotide variant has a sensitivity and specificity of 97.9 percent and 100 percent, respectively. (The study authors note that this compares favorably with the 88.3-percent sensitivity achieved by whole-exome sequencing using a commercially available exome capture set; they attribute this to better coverage of targeted genes in the GEDi tests.) Prospective testing of 192 patients with inherited retinal degenerations found that the retinal GEDi test had a diagnostic rate of 51 percent.

These tests can be ordered by a medical professional; turnaround is 90 days. The retinal test costs $2,500; the atrophy/glaucoma test costs $1,250. (Health insurance may cover part or all of the cost.)

Another recent development is an advanced DNA test relating to congenital cataracts, a condition that can be a symptom of more than 100 different diseases. Uncovering the mutations linking the congenital cataracts to those diseases used to be a long, costly and not totally reliable process involving multiple genetic tests and numerous non-genetic tests, guided by a detailed family history. Now, researchers at the University of Manchester in England have developed a test using a new DNA-sequencing technology called next-generation sequencing, or NGS. The new test looks at 115 genes known to be associated with congenital cataracts and can find mutations connected to one of those diseases within a few weeks. (The new test has also uncovered mutations related to the condition that were not previously known.)

A study assessing the efficacy of the test, recently published in *Ophthalmology*,[2] involved 36 patients diagnosed with bilateral congenital cataract (nonsyndromic or syndromic) and a control group. The test was able to determine the genetic cause of the congenital cataract in 75 percent of the subjects. Furthermore, 85 percent of patients with nonsyndromic CC had likely pathogenic mutations.

"Congenital cataract is a difficult condition to diagnose genetically; more than 100 genes have been as-

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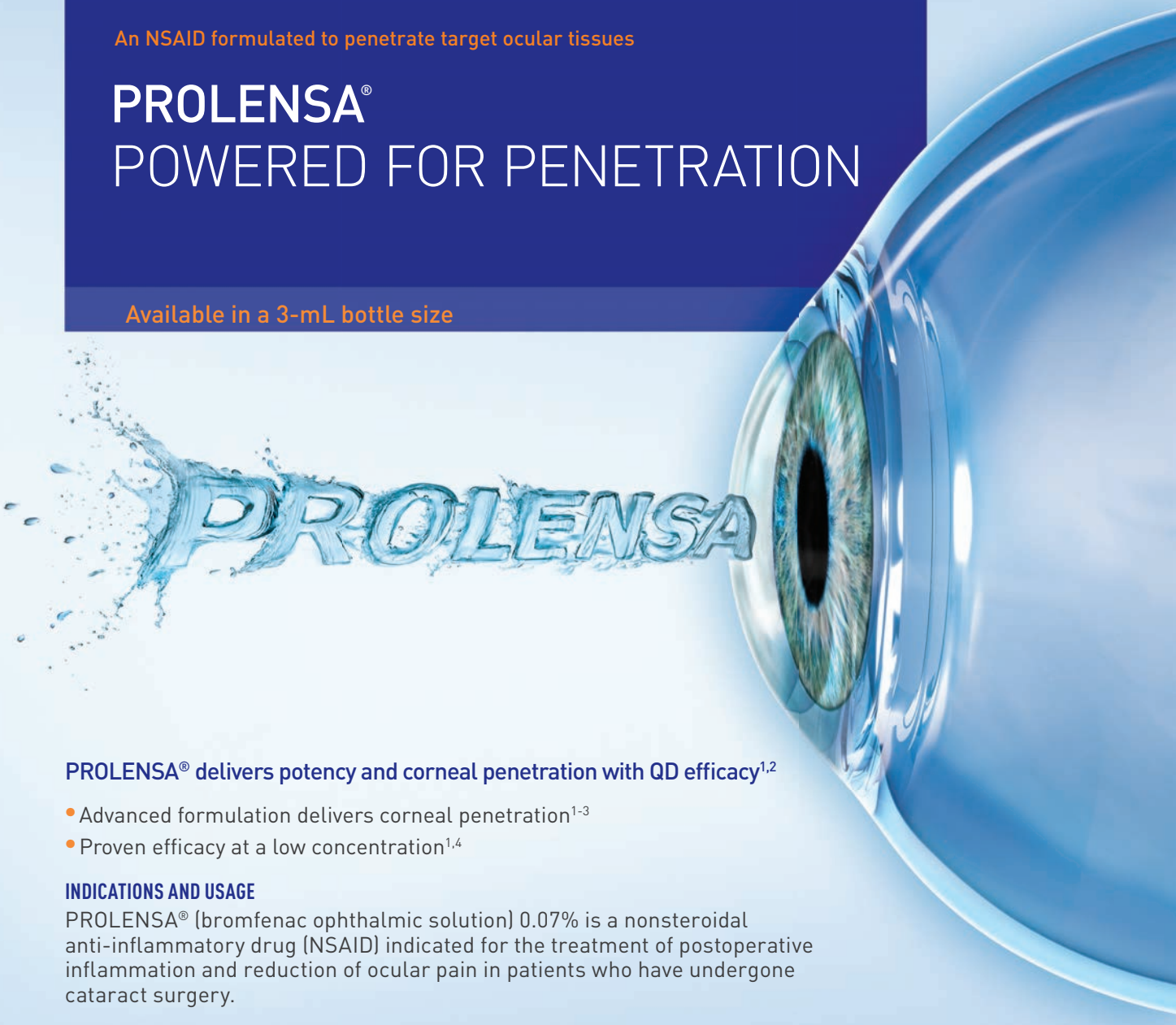

PROLENSA® delivers potency and corneal penetration with QD efficacy[1,2]

- Advanced formulation delivers corneal penetration[1-3]
- Proven efficacy at a low concentration[1,4]

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

Warnings and Precautions

- Sulfite allergic reactions
- Slow or delayed healing
- Potential for cross-sensitivity
- Increased bleeding of ocular tissues
- Corneal effects, including keratitis
- Contact lens wear

Adverse Reactions

The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

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

References: 1. PROLENSA® Prescribing Information, April 2013. **2.** Data on file, Bausch & Lomb Incorporated. **3.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of ^{14}C-labeled bromfenac following topical instillation into the eyes of New Zealand White rabbits. *J Ocul Pharmacol Ther.* 2008;24(4):392-398. **4.** BROMDAY® Prescribing Information, October 2012.

BAUSCH + LOMB

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

Use with Other Topical Ophthalmic Medications

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

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

Slow or Delayed Healing

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

Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time

With some NSAIDs, including bromfenac, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that PROLENSA® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

PROLENSA should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

ADVERSE REACTIONS

Clinical Trial Experience

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

The most commonly reported adverse reactions following use of PROLENSA® ophthalmic solution following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia and vision blurred. These reactions were reported in 3 to 8% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

Treatment of rats at oral doses up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality and reduced postnatal growth at 0.9 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of PROLENSA® ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when PROLENSA is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

Geriatric Use

There is no evidence that the efficacy or safety profiles for PROLENSA differ in patients 70 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively, revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents.

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

Concomitant Use of Contact Lenses

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

Concomitant Topical Ocular Therapy

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

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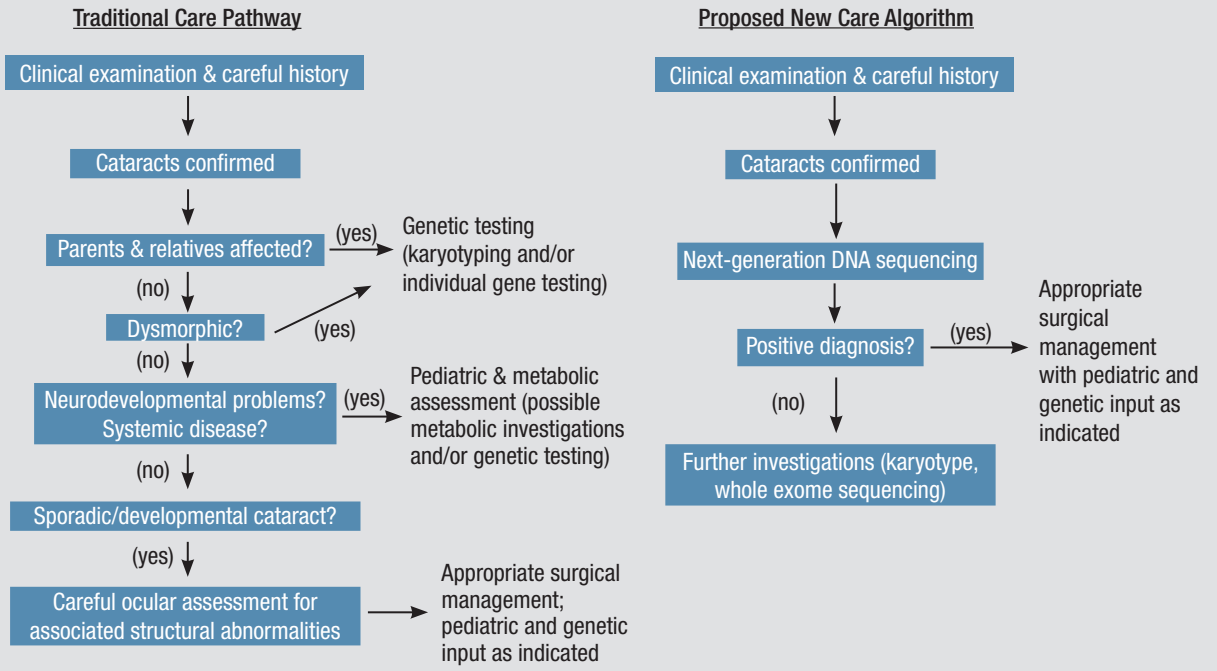
Care Pathways for Child Suspected of Congenital Cataract



Use of next-generation DNA sequencing—which screens 115 cataract genes simultaneously from a single sample—holds the promise of a quicker diagnosis for many patients, leading to earlier treatment and potentially better outcomes. (Based on Gillespie RL, et al, 2014.[2])

sociated with it," notes Rachel Gillespie, who designed the new test and is lead author of the study. "Importantly, cataracts in children and babies can present as an isolated problem or as an early indication of an underlying multi-system condition. However, clinical presentations in infants and young children can be very mild and ambiguous, so delineation of the precise cause is almost impossible. [At the same time,] prompt diagnosis of these conditions is imperative so that early preventative treatment and/or disease monitoring can commence as soon as possible.

"Traditional genetic testing methods would require screening of cataract-causing genes individually and consecutively to find the cause—a process that can take a very long time and is often unsuccessful," she continues. "Our test screens 115 cataract genes simultaneously from a single small blood or saliva sample, making diagnosis much easier and more efficient. We have seen a very high diagnosis rate: Our test is able to find the likely cause in about 75 percent of all patients tested. Interestingly, for a number of children, our genetic findings have enabled a diagnosis of specific conditions, altering their clinical management and treatment. Furthermore, identification of the genetic cause of congenital cataract within families enables counseling for prognosis, the risk to other family members and advice on prenatal testing in future pregnancies.

"For example, one family we worked with had three members—two brothers and their cousin—who presented with childhood-onset cataracts, seizures and challenging behavior with autistic features that seemed to be worsening with age," she says. "They had each undergone numerous tests to try and determine the cause, and despite additional findings of delayed myelination from an MRI scan, a precise diagnosis was not made. NGS genetic screening identified a mutation in the gene CYP27A1 that is known to cause cerebrotendinous xanthomatosis, a lipid-storage disorder that can be fatal; we confirmed this mutation as pathogenic by lipid profiling. CTX is very mild in infancy (initial presentations are cataract and diarrhea), but becomes much more serious with age. Early diagnosis is crucial because preventative treatment is available in the form of chenodeoxycholic acid and statins, which may prevent disease progression but cannot reverse it later on. Luckily, we were able to diagnose this condition relatively early in this family and they are all doing well on treatment."

Ms. Gillespie says they've been working hard on this new technology. "We're currently researching the impact this test is having on the care of congenital cataract patients," she says.

"The test has been available in the U.K. since December 2013, and it can be requested by registered medical facilities via international referral on a diagnostic (rather than research) basis. Referral information can be found at mangen.co.uk, along with sample criteria. To conduct the test we ask for either a minimum of 1 ml of blood in EDTA (Ethylenediaminetetraacetic acid), or 10 µg of high-quality DNA."

Making Testing Accessible

Another laboratory doing notable work is The John and Marcia Carver Nonprofit Genetic Testing Laboratory, affiliated with the University of Iowa. The lab, headed by Edwin M. Stone, MD, PhD, and Val C. Sheffield, MD, PhD, is dedicated to providing non-profit genetic testing for rare eye diseases. The tests they offer incorporate the research done by Drs. Stone and Sheffield, so the tests provide the most clinically relevant information while remaining affordable.

"When I started working for the Carver Lab there were probably 20 inherited eye disease genes known," says the lab's Jean Andorf. "Now there are more than 250. So the field has grown fast, and our testing has grown with that gene discovery rate. We were motivated to offer these services because once a gene has been found and studied for a long time you can't take grant money for the purpose of genotyping more families. So, all these research dollars would go to discover a gene, and then the genetic testing wouldn't be available for the patients. Our goal was—and still is—to offer affordable genetic testing to anyone who wants it. What we charge for a test is truly just the cost of the lab technicians and the reagents.

"We are also a research lab," she continues. "About a third of our effort focuses on nonprofit genetic testing; and about two-thirds is on research. We're constantly looking for new genes, as well as ways to better understand the genes that are known. For example, one of our biologists, Budd Tucker, PhD, is making huge strides in using pluripotent stem cells to treat people with inherited eye diseases."

> *"A lot of unnecessary testing results from physicians not trusting their own diagnosis. Our goal is not to diagnose the patient ... [but] to confirm the diagnosis."*
> *— Jean Andorf*

One of the projects under way at the Carver Lab is referred to as "Project 3,000," an effort to identify every person in the United States suffering from Leber's congenital amaurosis—estimated to be about 3,000 in number. "This program has allowed us to offer genetic testing to these individuals and populated a number of the RPE65 treatment trials, while providing a significant population for future clinical research into long-term prognosis," says Ms. Andorf. "In addition to finding most of the LCA patients under the age of 20, we've also identified a handful of older people with the disease. Some didn't realize they had this disease; many were simply born blind during an era when little was known about inherited eye diseases. Many of these adults are cognitively normal with high intelligence and functioning very well. That enables us to give hope to families with a child sharing that particular genetic cause. You can say, 'I have a 70-year-old patient who did just fine in her life who has the same type of genetic mutation as your child.' That kind of information is hugely beneficial for a family, even if it doesn't bring them treatment today."

Making the Most of Testing

Ms. Andorf offers several suggestions regarding genetic testing:

- ***Your patient may not need complete exome testing.*** "Thanks to the existence of exome sequencing, many laboratories will simply give you all of the data they find," she notes. "However, there are several diseases that are caused by one small gene or just a few genes. A whole exome costs several thousand dollars, whereas a test for that one mutation may cost a couple hundred dollars. While exome sequencing certainly has a place in genetic testing for inherited eye diseases, it's not a good use of anyone's resources to do a complete exome sequencing for a person with a monogenic disease."

Ms. Andorf says a lot of unnecessary testing results from physicians not trusting their own diagnosis. "We really want doctors to order the right test," she says. "It's not good for us if a doctor orders multiple tests on our website for a patient because he's trying to find a diagnosis. Doctors have been seeing most of these patients for a long time; they need to trust their clinical expertise to try to match the patient's clinical findings with the appropriate test. Our goal is not to diagnose the patient through testing; our goal is to confirm the diagnosis. In fact, we're working on sharing clinical information with physicians that will help them narrow down the testing for their patients."

Ms. Andorf says that for this reason, they often screen patients who have heterogeneous diseases in tiers. "We start by testing for the most likely genetic mutation," she explains.

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INDICATION FOR USE. The iStent® Trabecular Micro-Bypass Stent (Models GTS100R and GTS100L) is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication. **CONTRAINDICATIONS**. The iStent® is contraindicated in eyes with primary or secondary angle closure glaucoma, including neovascular glaucoma, as well as in patients with retrobulbar tumor, thyroid eye disease, Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS**. Gonioscopy should be performed prior to surgery to exclude PAS, rubeosis, and other angle abnormalities or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. The iStent® is MR-Conditional meaning that the device is safe for use in a specified MR environment under specified conditions; please see label for details. **PRECAUTIONS**. The surgeon should monitor the patient post-operatively for proper maintenance of intraocular pressure. The safety and effectiveness of the iStent® has not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, chronic inflammation, or an abnormal anterior segment, in pseudophakic patients with glaucoma, in patients with pseudoexfoliative glaucoma, pigmentary, and uveitic glaucoma, in patients with unmedicated IOP less than 22 mmHg or greater than 36 mmHg after "washout" of medications, or in patients with prior glaucoma surgery of any type including argon laser trabeculoplasty, for implantation of more than a single stent, after complications during cataract surgery, and when implantation has been without concomitant cataract surgery with IOL implantation for visually significant cataract. **ADVERSE EVENTS**. The most common post-operative adverse events reported in the randomized pivotal trial included early post-operative corneal edema (8%), BCVA loss of ≥ 1 line at or after the 3-month visit (7%), posterior capsular opacification (6%), stent obstruction (4%) early post-operative anterior chamber cells (3%), and early post-operative corneal abrasion (3%). Please refer to Directions for Use for additional adverse event information. **CAUTION**: Federal law restricts this device to sale by, or on the order of, a physician. Please reference the Directions for Use labeling for a complete list of contraindications, warnings, precautions, and adverse events.

"In a significant percentage of patients we identify the mutation with a single, inexpensive test using this protocol. The other advantage of this approach—which some people criticize us for—is that a complete exome reveals a lot of irrelevant information that can cloud a diagnosis. We screen the gene most consistent with your clinical features.

"It's even more important to have a diagnosis that's as accurate as possible when pursuing exome sequencing," she adds. "On average, exome sequencing will reveal very plausible disease-causing mutations in eight known inherited eye disease genes. Thus, patients with inaccurate diagnoses will often have misleading findings in genes consistent with the inaccurate diagnosis. We've seen cases in which families and physicians have been misled because of this type of situation. Too much genetic information can make the results harder to interpret."

• ***Make sure the patient is consulting with a genetic counselor.*** "Lots of patients e-mail us reports that they got from another lab—a list of mutations with no interpretation of the findings," says Ms. Andorf. "Here, we work with an inherited eye disease specialist who has dealt with inherited eye disease for more than 25 years. Whatever disease you're dealing with, we've probably screened thousands of others with the same disease. Having the ability to see clinical correlations to genetic test results gives you a higher level of confidence in the interpretation and minimizes information that may be confusing.

"For that reason, the physician requesting a test from us has to write down who is providing genetic counseling to the patient," she says. "Patients often want us to send the report directly to them. We say, 'If your doctor ordered a kidney function test for you, the lab wouldn't send the results directly to you. You really need to have a physician and a genetic counselor to be able to understand these data.' We try to get the physician and family to think about that in advance of the test."

• ***Turnaround time should not be your only consideration.*** "We are sometimes criticized for our long turnaround times," notes Ms. Andorf. "That's true in some cases, but we group patients together in order to keep the costs as low as possible. And we're not just a clinical laboratory. Some services will offer a complete exome sequencing within four weeks, but we believe it makes more sense to order a specific test that's in line with your own diagnosis, even if it takes longer to receive the results."

Locating Resources

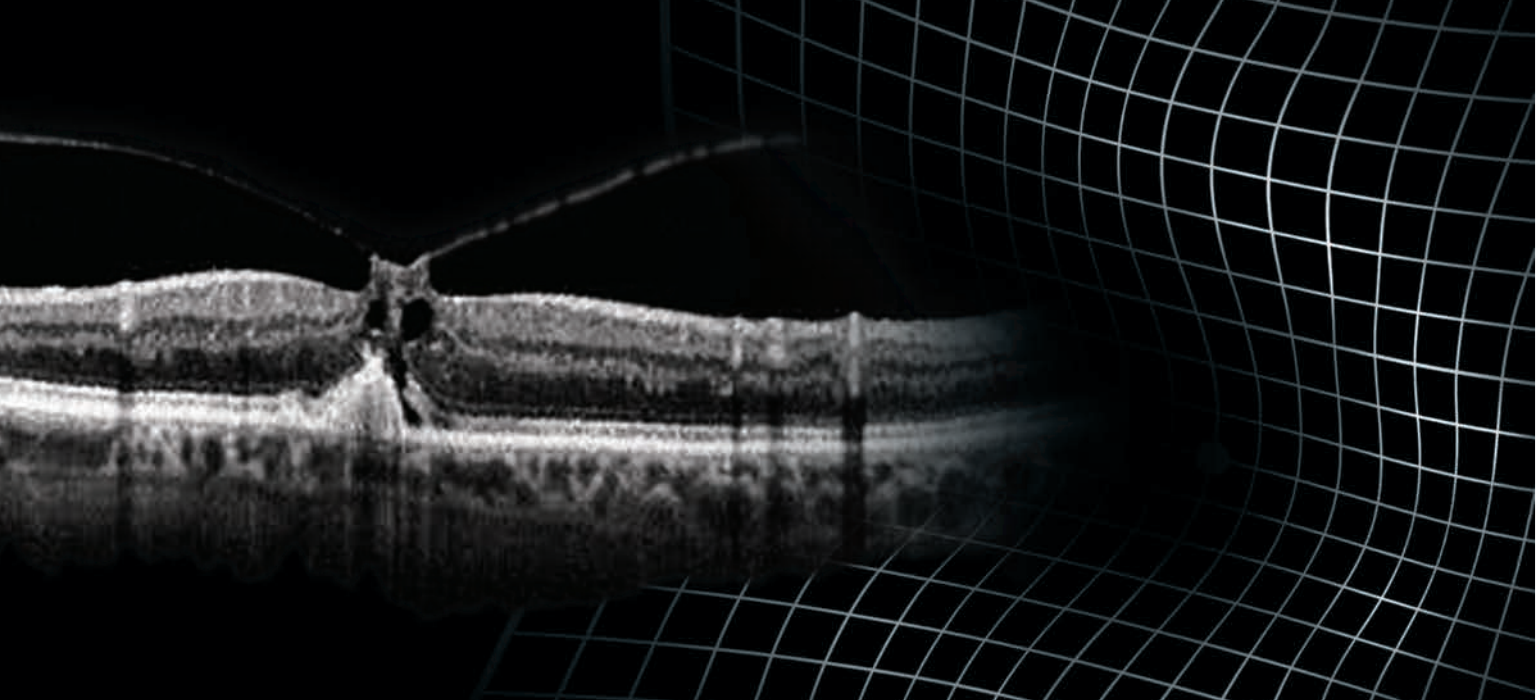
As the number of tests available increases, along with the number of laboratories offering the tests, the need for a central clearinghouse has become evident. One company attempting to meet that need is GeneTests, based in Elmwood Park, N.J. Its mission is to promote the appropriate use of genetic testing by providing current, easy-to-access, free information about test availability.

According to Deborah L. Eunpu, manager at the company, the most commonly requested genetic tests relating to eye disease include tests for Leber's congenital amaurosis; optic atrophy; retinitis pigmentosa; retinoblastoma; age-related macular degeneration; oculocutaneous albinism; congenital cataracts; congenital glaucoma; malformations of the eye (e.g., aniridia, microphthalmia, anophthalmia); and dislocated lens. Ms. Eunpu says that once a surgeon has found a laboratory that offers the services in which the surgeon is interested, he can contact the lab directly. "On our website, once a test is selected, information about the laboratory can be accessed via the information listed with the test," she explains. "Some labs include links to their test page or requisition forms that can be downloaded. We ask the labs to provide turnaround times, and they are often available on the test information page. Some tests may take less than a week—for example, some biochemical tests, or fluorescence *in situ* hybridization [a test that allows visualization and mapping of the genetic material in an individual's cells]—but others, such as full exome sequencing, may take up to 16 weeks. The technology determines the time the test takes."

Ms. Eunpu notes that test usage is increasing, and options for testing continue to expand. "In the past year we've added nearly 10,000 new tests, many due to new technologies," she says. "For example, the availability of next-generation sequencing has opened the door to testing multiple genes at a time. These tests can be most helpful if one is not sure which of several related conditions to test for. However, when a specific diagnosis is suspected, a single gene can be interrogated."

Ms. Eunpu expects to see even more new tests and increased usage. "Genetics continues to be an exciting, evolving field in which advances in technology and knowledge can lead to rapid changes," she says. "Will everyone have full sequencing? Not likely. But as more treatments are based on knowing the specific genetic mutation, the reasons to do many tests will be compelling. With clinical trials and opportunities for improved vision arising through emerging treatments, testing is being looked at much differently. Now testing may lead to specific treatments." REVIEW

1. Consugar MB, Navarro-Gomez D, Place EM, et al. Panel-based genetic diagnostic testing for inherited eye diseases is highly accurate and reproducible, and more sensitive for variant detection, than exome sequencing. Genet Med. 2014;Nov 20. [Epub ahead of print.]
2. Gillespie RL, O'Sullivan J, Ashworth J, et al. Personalized diagnosis and management of congenital cataract by next-generation sequencing. Ophthalmology 2014;121:2124-2137.



SYMPTOMATIC VITREOMACULAR ADHESION (VMA)

SYMPTOMATIC VMA MAY LEAD TO VISUAL IMPAIRMENT FOR YOUR PATIENTS[1-3]

IDENTIFY | Recognize metamorphopsia as a key sign of symptomatic VMA and utilize OCT scans to confirm vitreomacular traction.

REFER | Because symptomatic VMA is a progressive condition that may lead to a loss of vision, your partnering retina specialist can determine if treatment is necessary.[1-3]

THE STEPS YOU TAKE TODAY MAY MAKE A DIFFERENCE FOR YOUR PATIENTS TOMORROW

ThromboGenics®

References: 1. Sonmez K, Capone A, Trese M, et al. Vitreomacular traction syndrome: impact of anatomical configuration on anatomical and visual outcomes. *Retina*. 2008;28:1207-1214. **2.** Hikichi T, Yoshida A, Trempe CL. Course of vitreomacular traction syndrome. *Am J Ophthalmol*. 1995;119(1):55-56. **3.** Stalmans P, Lescrauwaet B, Blot K. A retrospective cohort study in patients with diseases of the vitreomacular interface (ReCoVit). Poster presented at: The Association for Research in Vision and Ophthalmology (ARVO) 2014 Annual Meeting; May 4-8, 2014; Orlando, Florida.

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Who's Getting Femto Laser Cataract Surgery?

Christopher Kent, Senior Editor

Surgeons who use this technology share their experience with patient and economic issues.

The use of femtosecond laser technology to perform key parts of cataract surgery (e.g., incisions, capsulotomy and softening the nucleus) continues to be controversial—not because of any problem with the technology, but because it's expensive relative to the perceived amount of improvement it brings to the procedure. Compounding the problem, reimbursement from insurance companies and Medicare is very limited. As a result, many surgeons are hesitant to invest in the technology.

Questions that arise when surgeons consider adding this to their armamentarium include: Will there be enough reimbursable uses to make the purchase worthwhile? Will patients be willing to pay extra for the technology to be used? How much does the economic status of your patient base matter? And is it possible to earn back the cost of the equipment in a reasonable amount of time? Here, three surgeons who have used this technology for several years share their experiences.

When Is the Laser Being Used?

Karl Stonecipher, MD, medical director for TLC Laser Eye Centers in Greensboro, N.C., and clinical associate professor of ophthalmology at the University of North Carolina, explains that there are three situations in which most surgeons who have access to the technology use a femtosecond laser to perform cataract surgery: as part of a premium procedure; in response to surgical concerns; or for its diagnostic capability—specifically, optical coherence tomography. "We cannot get reimbursed for using the laser, per se," he notes. "So if you're using femtosecond laser for cataract, the patient is probably getting a premium lens of some kind—toric, multifocal or accommodating. Most surgeons don't use femtosecond laser for a standard procedure.

"Of course, there are exceptions to that rule," he continues. "I'll perform femtosecond laser cataract surgery if I have someone on Flomax, or someone with a white cataract, narrow angles, pseudoexfoliation, previous trauma or a previous vitrectomy; anything I think will make the surgery harder. Sometimes just using the laser minimizes a problem even if you couldn't see it coming. I recently put a lens in a patient and the lens dislocated inferiorly; I repositioned it and it dislocated again. On the third attempt I sutured it to the iris. It turned out the patient had a coloboma I couldn't see at the slit lamp. If I hadn't used the femtosecond laser, I would have had vitre-

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ous everywhere. It would have been a much more complex procedure."

Although the technology may be helpful in a therapeutic capacity, Dr. Stonecipher notes that this raises some questions. "Which patients really need it?" he asks. "Should you use it for every case that's complicated? I think the laser has been shown to put less stress on the eye. It allows me to do the lion's share of the procedure before I even go into the eye. If I can make the incisions, do the capsulotomy and soften the lens before I enter the eye, that's going to make it easier for me to take that lens out."

The other way to get reimbursed for use of the laser is to charge for using its OCT as a diagnostic aid—to check the condition of the zonules, for example. Dr. Stonecipher says the diagnostic OCT has helped him avoid trouble in numerous cases. "Recently I discovered that a patient had zonular dehiscence from trauma," he says. "The patient never told me about it, and all I saw at the slit lamp was a little phacodonesis. Because of the OCT, I was prepared to put in a capsular tension ring prior to entering the eye, and that prevented a very complex surgery.

"The bottom line," he says, "is that we can charge for the diagnostics; we can use the femtosecond laser as part of a premium channel package; we can charge for astigmatic surgery that uses the laser; we can charge for the premium IOL that is implanted with the help of the laser; but we can't charge for the laser itself."

All images: Y. Ralph Chu, MD

Many surgeons are using femtosecond laser cataract surgery as part of a premium channel offering; to help manage challenging surgical situations; or when its optical coherence tomographer can help visualize surgical issues (a use that is reimbursable, pictured above).

Which Patients Want the Laser?

Of course, in many cases using the laser means more cost to the patient. That raises a key question: Under what circumstances are patients willing to agree to the added cost?

Y. Ralph Chu, MD, founder and medical director of Chu Vision Institute in Bloomington, Minn., and adjunct associate professor of ophthalmology at the University of Minnesota, says that currently 50 to 60 percent of his cataract surgery patients receive femtosecond laser cataract surgery. He believes the primary reason patients are open to considering femtosecond laser cataract surgery is the desire for a refractive result rather than a medical result.

"To me, cataract surgery can be seen as falling into two categories," he explains. "For some patients it's simply a medical procedure in which we're removing a lens and putting in an implant, followed by basic refractive care, which means glasses. On the other hand, if the patient wants the ability to function as best he can, whether at distance or at near, without glasses—or at least with less dependence on glasses—that becomes refractive cataract surgery. Patients in the latter category are open to being educated and choosing to receive new technologies like femtosecond surgery, use of the ORA device and other technologies."

Of course, many surgeons are concerned that their patients will balk at paying extra money for the use of the laser, but most surgeons using the technology seem to agree that this is less of an issue than they expected. Inder Paul Singh, MD, president of the Eye Centers of Racine and Kenosha in Wisconsin, notes that the part of the country in which he practices is not affluent and was hit fairly hard in the recent economic downturn. Nevertheless, he finds that many patients are interested in being treated with advanced technology, even if the cost is higher. (He offers the use of the laser during cataract surgery as a premium service for patients who would like to have it, in addition to those who need arcuate incisions or might have it bundled into a premium intraocular lens package. He does not own the laser himself; he convinced a local hospital to invest in the technology, and he takes his patients there for the surgery.) "Right now we have a 60- to 65-percent adoption rate in our area," he says. "I don't sell it, I don't promote it, I don't advertise it. We just educate patients about it in our office."

Is it possible to predict which patients are more likely to agree to pay extra for more advanced technology? Dr. Chu says no. "You cannot judge a book by its cover," he notes. "We get a wide range of patients who choose to do this kind of procedure, and their financial status may have nothing to do with it. It's more of an attitude thing.

"One day, for example, I had two patients come in; one was a school lunch lady, the other was the CEO of a company," he says. "You might have thought the CEO would have chosen to have the best technologies used in his surgery regardless of the cost, but his attitude was one of extreme frugality. That's how he ran his company. So he chose not to do a premium IOL or any lasers. On the other hand, the school lunch lady said, 'You know, I've never bought anything for myself, and this is the one thing I want to buy to improve myself.' She wanted to be able to lift the covers on the food and not have her glasses fog up, so she could see the kids as she delivered the food to them. She got a great result with a premium lens and the lasers. So she's happy—and he's happy too. That experience acts as a reminder to me that I should never restrict which patients are introduced to these technologies, and that everyone deserves to know their options so they can make the best choices for themselves. After all, this is elective surgery."

Dr. Singh also says he doesn't assume anything about what a given patient may be willing or able to pay. "My job is not to sell premium procedures," he says. "However, a lot of patients say, 'Doc, what would you do?' I say, 'You know what? If it wasn't for the money, I'd say why not do this? Why not have a precise capsulotomy and a precise arcuate incision and have less total ultrasound energy in the eye?' I tell them if it wasn't for the money, I wouldn't be giving them a choice; I'd just use the more advanced technology. I really do believe it's a better option for my patients.

"I tell patients that I'm not here to tell them what they can or cannot afford," he continues. "Some patients ask me if they need to have the laser. They say, 'I'll mortgage my house to use the laser if you think it will make a big difference for me.' I tell them that manual cataract surgery is still a very good, predictable surgery for the most part; they don't have to have the laser. I'll take good care of them either way. I try to be honest and let them know whether or not I think it will make a significant difference. If it's a young person with an early cataract getting a standard lens with half a diopter of astigmatism, I can do manual LRIs and get a good result. I think you have to use your judgment, and you have to be honest when you help the patient make a decision."

"If a patient expects to have a perfect outcome because of the laser, that's a contraindication."
—Inder Paul Singh, MD

Dr. Singh admits that he does see a difference in the interest level of different age groups. "Patients who are younger than 65 tend to want to have the laser," he says. "Patients who are 75 or 80-plus tend to say, 'I'm not really worried about whether I have to wear glasses or if I have a couple extra weeks of recovery. It's OK, I can deal with that.' Younger patients are more inclined to want the latest, best technology. They're the iPad and iPhone users who think that if it's newer, it's got to be better. Some patients come into our office saying, 'Doc, give me the best technology, I don't care what it is.' I say, 'Wait—let's talk about it.' They say, 'No that's fine, just do it.' "

Contraindications

Clearly, even if a patient is interested and/or willing to pay for this technology to be used, he might not be a good candidate, either for medical or psychological reasons. "If the patient has the desire to have a refractive outcome," says Dr. Chu, "then we ask a series of questions to determine whether she is a good candidate: Are her eyes healthy enough to achieve value from those extra technologies? Does she have macular degeneration or corneal pathology like basement membrane dystrophy, or a scar or glaucoma? I don't think any one of those things is an absolute contraindication, but these are things the surgeon and patient have to consider when they're thinking about femtosecond laser cataract surgery."

"Medical contraindications would include corneal issues such as scarring that could interfere with docking; keratoconus; glaucoma surgery blebs; people who have corneal pannus, where you're not going to be able to do a good corneal or arcuate incision; cases in which you don't have good visualization of the extracapsular area; and patients with small pupils that might prevent a good capsulotomy or fragmentation pattern," says Dr. Singh. "All of these medical conditions are a reason to say no. I'd also say no to a patient who is fidgety and apprehensive in general. You don't want the patient shaking under the laser.

"From more of a psychological perspective, I think patients who have unrealistic expectations are a potential problem," he says. "If the patient expects to have a perfect outcome because of the laser, that's a contraindication. If they say they'll pay more money if I can guarantee something, I wouldn't want to go that way. I don't want to use the laser and have them not get the outcome they're expecting and then demand to know why."

Dr. Chu agrees that unrealistic expectations could disqualify a patient, but believes that's not limited to this situation. "I think that's probably true across the board for eye care," he says. "This is elective surgery. I think it's

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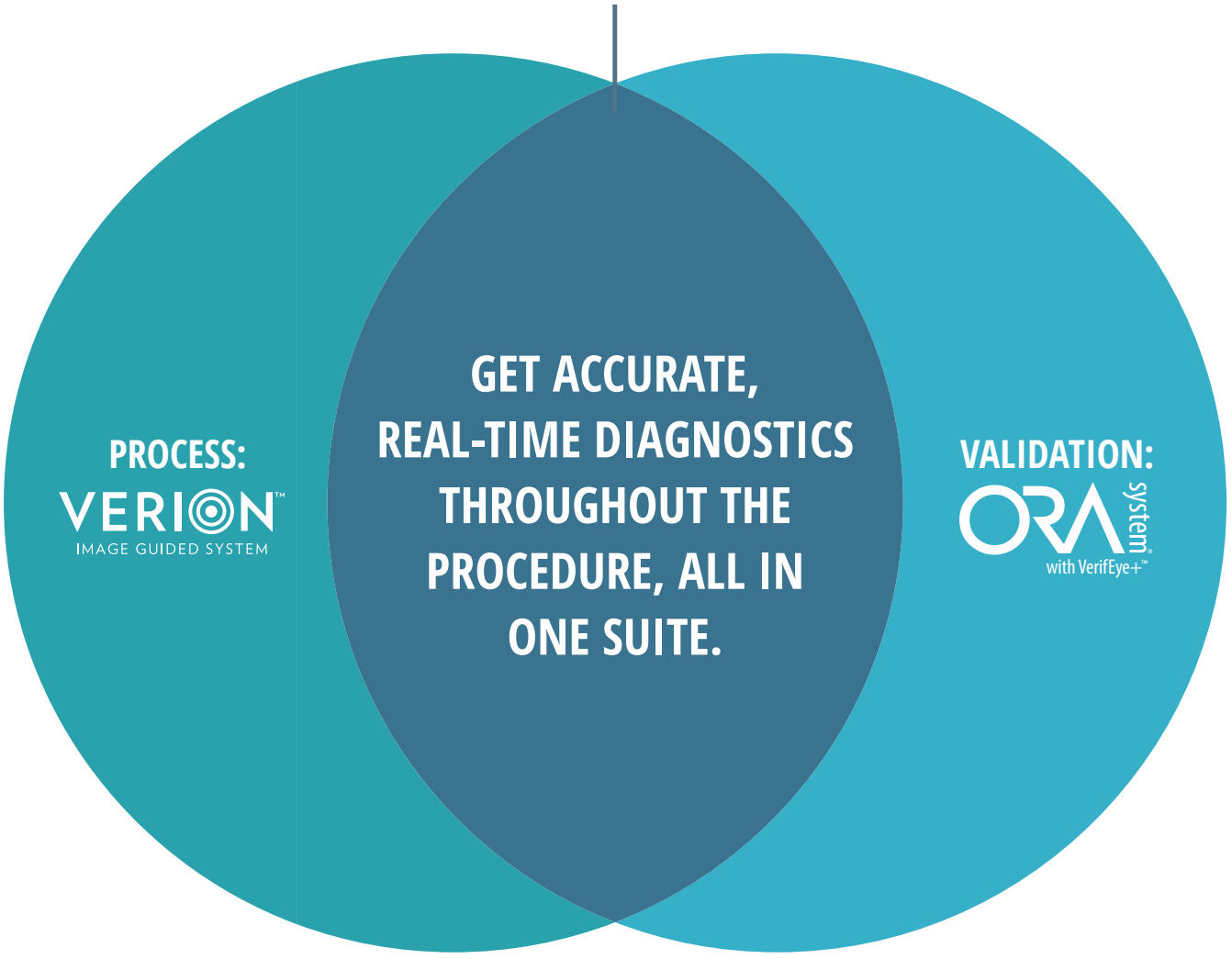

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important to assess whether someone has unrealistic expectations before surgery whether he's getting the femtosecond laser or not. Some of our most difficult patients are those who haven't chosen the femtosecond laser at all. They expect a refractive outcome because that's what their friends got, even though they don't opt for refractive cataract surgery using the best technology."

Patients Who Ask for the Laser

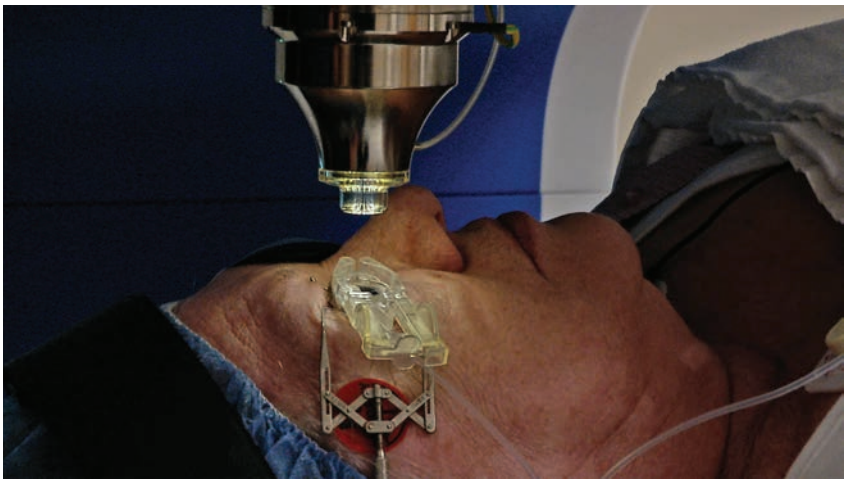
Dr. Chu notes that an increasing number of patients are coming in asking specifically for femtosecond laser cataract surgery. "We're seeing more and more of that," he says. "As patients are forced to be more responsible for where their health-care dollar goes, they're starting to look around more. And word does get out that these technologies exist. Patients are interested in seeing better, and they like the concept of laser surgery in general. I think the technology is showing that it can deliver, so if a patient comes in requesting it, that makes the discussion about the options pretty easy.

"On the other hand, you have to be careful," he continues. "Many patients can't afford the technology, and even if they find the idea appealing, they may not be looking for a refractive result. Right now, we can't get reimbursed for using the laser unless we're correcting astigmatism or utilizing the intraoperative imaging for a premium IOL; meanwhile, there's a cost to the practice each time the laser is used. Ultimately, it's up to the surgeon to use the tools needed to get the best outcome, whether the laser is reimbursed or not."

Dr. Singh says that recently people have started coming into his practice specifically asking for the laser. "I've had access to the laser for a year and a half," he notes. "It wasn't until about a year after I started performing femtosecond laser cataract that I started seeing patients come in saying they'd heard about the laser and wanted it. Clearly, when a critical mass of patients has had it done, that has a marketing effect.

"It's important to tell patients when you believe the use of the laser made a real difference in the outcome," he continues. "I had a patient who had 2.5 D of cylinder; he wanted a special lens and it didn't come in his power. So I had to make arcuate incisions to eliminate a lot of the astigmatism. He ended up 20/20. I said to him, 'You would not be 20/20 if it wasn't for those arcuate incisions I made with the laser, so the laser really did help you see better.' He told his brother, who came in and wanted the laser as well. If the laser really does make a difference and you point that out and explain why, a happy patient will become your advocate out in the community.

"Of course, there have been some patients where I



A few surgeons in the United States have tried performing femtosecond laser cataract surgery on every patient, but the limited reimbursement options have made it a challenge to remain profitable, even with increased volume.

made a small arcuate incision with the laser that may or may not have made a difference in their quality of vision afterwards, but they're happy that they got the laser and tend to assume the laser deserves the credit," he continues. "I'm careful with those patients, because part of my job is to be fair and balanced. So I don't tell them it's because of the laser that they got their outcome. On the other hand, if a patient had a pseudoexfoliation issue or a tough capsule or a dense cataract, I will tell him that if he'd had a standard surgery, more than likely I would have had to use more energy inside the eye and he might have had less-sharp vision the next day. So in certain circumstances I will tell the patient that the laser made a difference. For the average patient I just say that I'm glad it went well."

Dr. Stonecipher says he has also seen patients come in asking for the laser. "Of course, even patients who want the laser may have a problem affording it," he notes. "You have to provide financing options for those patients. That's another one of the options you have to offer in order to have success with the femtosecond laser."

What about simply performing femtosecond laser cataract surgery on every cataract patient? "A few people have tried using the laser on every cataract patient," Dr. Stonecipher says. "Shachar Tauber, MD, is still doing that and says his practice is making it work with volume by attracting many patients and community surgeons. But trying to do femtosecond laser on everybody without charging for a premium channel means you're losing $350 a case. If you're only making $350 a case, how's that going to work out? You can't compensate for that with volume. My partner tried using that business model, but it didn't work. Without charging a premium to offset the laser fee it was just economically unworkable."

Presenting the Option

Surgeons have differing opinions regarding whether the option of having femtosecond laser cataract surgery should be presented to every patient. Of course, the extra cost weighs heavily in that debate. "A lot of people desire refractive outcomes, but insurance covers less and less nowadays," notes Dr. Chu. "So we have to talk about the cost. Patients have to pay more and more even for basic care, let alone some of the newer technologies, whether it's lasers, implants or new pharmaceuticals. So cost becomes part of the discussion and part of the decision tree for patients. Unfortunately, cost is going to be an increasingly important factor in decision-making in every aspect of health care.

"We're not offering this option because we want to make more money," he continues. "We want our patients to have as many options as possible, and when we talk to them we want to make sure they know about every option. I feel that if a patient isn't educated and told about all of the available IOL options and all available technologies, including the excimer laser that can be used after cataract surgery to enhance the cataract surgery outcome, that's a shame. So we're passionate about education and letting patients make the best choices for themselves. We say to the patient, here's the technology that's available. There's refractive cataract surgery and non-refractive cataract surgery. Here's the technology that helps us achieve the result, and here's the cost. It's pretty straightforward, and there's no pressure on the patient to choose one option over another. Patients have no problem telling us they don't want to buy something.

"I'd feel bad if a patient who is interested in refractive cataract surgery or astigmatism correction said no one had told him about these technologies," he adds. "I think that happens in a lot of practices. Sometimes patients come to us after having had surgery elsewhere and say, 'Gosh, I wish I'd known about this.' They may end up feeling like you hid something from them. So I'm really passionate about patients knowing that we offer all of these options, even if the patient isn't a good candidate. If that's the case, we still explain all the options, we just also explain that the patient isn't a good candidate for this one or that one, and why."

Dr. Stonecipher says that he used to

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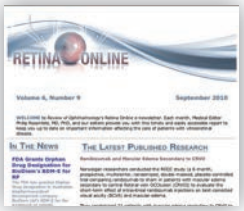

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tell every patient about the laser option, but no longer does. "I believe all our patients know that it's an option," he says. "It comes up somewhere in the discussions the patient has with staff members. But if I'm looking at you and you're glazed over and you say you love your glasses and can't afford anything, there's no reason to go through that discussion. Talking about the option when the patient doesn't want it or can't afford it is just going to make the patient feel bad or believe you're doing an inferior procedure.

"I tell my patients that I'm going to treat them as if they were members of my own family and do what I think is best for them," he says. "If the patient is a candidate for a premium channel, I ask two questions: Do you want to be free of glasses? And if so, are you willing to pay for it? A lot of people say, 'No, I'm fine, my wife wouldn't recognize me without glasses!' But if they say yes, then I have to explain why they need that better technology and, if necessary, offer suggestions as to how they can afford it.

"The other side of the coin is patients in whom I want to use the laser to make the surgery safer or easier," he continues. "I do tell those patients about it. I may say, 'You've got pseudoexfoliation syndrome and that's going to make my job a little more of a challenge; I need you to let me use the diagnostics of this laser that costs $500 to help me do what I believe is a better surgery.' Some patients will refuse, so I document our conversation in the chart."

Dr. Singh sees several things as essential if you're offering femtosecond laser cataract surgery to your patients. "First of all, any time we ask patients to pay more for something, it's important to give them enough education about the benefits of that option to ensure that they understand its value," he says. "It's also important to make sure that everyone in the office is on the same page, because patients get information from everyone. That means you need to ensure that everyone provides similar answers when asked common questions like: What is cataract? What is astigmatism? What is a capsulotomy? What are the benefits of using the laser? Why is it important to have a perfectly centered, round capsulotomy? Why is it important to use less energy inside the eye? Why is it important to have astigmatism arcs that are perfectly cut to the exact depth? What do these factors mean for postoperative vision?

"Obviously we don't want to inundate patients with too much knowledge because that could get confusing,

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but I want to make sure they understand why this laser, in my opinion as a physician, is worth the extra cost," Dr. Singh says. "For me, education is the key. You can advertise all you want, but if patients don't understand it they won't be interested in it.

"The second thing that's really important for making patients feel comfortable about having this procedure done is to be excited about the technology yourself," he continues. "I don't mean that you have to go out there and cheerlead for it; but I think it's crucial that you believe in it. Doctors always say, 'I don't want to have to sell technology. I came here to be a doctor and do what's best for the patient.' I agree completely. If you don't feel that the technology offers any benefit, then you shouldn't be suggesting it. But if you feel that it does have some advantages, that's a different story.

"I certainly would not say that it's the right thing for every patient, or that every patient who has the femtosecond laser cataract procedure will have a better outcome," he adds. "That's not true. But I do tell patients that it helps me perform the procedure in a very predictable, precise way that may increase the likelihood of getting the best outcome. In my experience, that is true. So I believe if a patient can afford the more advanced technology, using it is worthwhile. You shouldn't apologize for the increased cost; just explain the benefits you believe the patient will gain so the patient can make his or her own decision."

But Is It Worth It?

Of course, many surgeons remain unconvinced that using the femtosecond laser as part of cataract surgery is worth the expense to the practice and the patient. Nevertheless, many who have used the laser disagree. "There are still a lot of surgeons out there that don't believe the femtosecond laser adds much to cataract surgery," says Dr. Stonecipher. "From my perspective, the femtosecond laser allows me to have a safer procedure when a case is potentially more complex. I think we're seeing more and more published articles saying the laser helps you with one thing or another. It makes you a better surgeon in some areas.

"Can I implant a multifocal IOL without the laser? Yes I can, but we're finding that effective lens position is really important in these patients," he continues. "If angle alpha—not angle kappa—is off enough, these patients are never going to see well. Using the

(continued on page 64)

Femtosecond Cataract: What the Data Says

Walter Bethke, Managing Editor

A review of how femtosecond-assisted cataract surgery is faring in the literature.

"I think most surgeons would recognize that femtosecond laser cataract surgery is brilliant—as long as they didn't have to pay for it," jokes Hyderabad, India, surgeon Kasu Prasad Reddy. Though Dr. Reddy uses the femtosecond in his practice, he acknowledges that his fellow surgeons have to think long and hard about investing hundreds of thousands of dollars in a device when they already get excellent results from conventional phacoemulsification. This thinking logically leads them to wonder what data exists on femtosecond that might shed some light on the kind of results they could expect with the new procedure. To help surgeons answer this question, following is a review of the major femtosecond research from the past several years, as well as thoughts from researchers on their findings.

Safety Signals

Some of the largest studies in femtosecond cataract have focused on the safety of the procedure.

In one of the few prospective, comparative studies of femtosecond cataract surgery vs. conventional surgery, surgeons from Tasmania performed femtosecond surgery on 1,852 eyes (the study group) and conventional surgery on 2,228 eyes (the controls). The researchers reported 34 tears in the anterior capsule (1.84 percent) in the study group vs. five in the control group (0.22 percent), a difference that was statistically significant (p=0.0001).[1] They noted that one case of anterior capsule tear in each group extended to the posterior capsule, necessitating an anterior vitrectomy. There were 21 incomplete capsulotomies in the laser group (1.13 percent) vs. none in the conventional patients, as well as 30 anterior capsulotomy tags (1.62 percent) with laser compared to 1 with conventional (0.004 percent; p=0.0001). The surgeons mention that just over half of the anterior radial and posterior capsular tears occurred in the later cases, which was one of the reasons why they didn't show a learning-curve effect during the study.

Posterior tear, the complication that surgeons are more concerned with than anterior rents, also occurred in both groups in the Tasmanian study. However, the authors say that despite eight posterior tears occurring in the laser group (0.43 percent) and four in the conventional group (0.18 percent), the difference wasn't statistically significant.

Tim Roberts, MBBS, MMed, consultant ophthalmic surgeon at the Royal North Shore Hospital, University

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of Sydney, believes that the paper by [the Tasmanian] group is important as it has "focused attention on the laser settings used and surgical techniques employed during laser cataract surgery." Dr. Roberts adds that, "From a surgeon's perspective, I believe the important question is not whether there are ultrastructural differences between manual and laser-cut capsulotomies, but what the clinical implication, if any, is of these differences." He points out that his group and others have found very low rates of anterior tears. "When you look at papers such as that by the Moorfields' group[2] and our own study,[3] you see other groups with large numbers aren't finding those high rates," he says.

In Dr. Roberts' study, he and his co-authors prospectively analyzed 1,500 femtosecond cataract cases, which they broke into two groups: 200 cases to get a sense of the initial skill level's impact on results; and then 1,300 to determine if experience with the procedure improved outcomes.

In the first group, the complication rates were higher. Eight cases (4 percent) had anterior radial tears, 21 (10.5 percent) had anterior capsule tags, seven (3.5 percent) had posterior capsule tears and four (2 percent) had posterior lens dislocation. Twenty-six patients (13 percent) had to have manual corneal incisions rather than laser-made cuts because the latter were impossible to make or could be made but not opened.

In the second group in Dr. Roberts' report, the rates went down: four (0.31 percent) had anterior radial tears; 21 (1.62 percent) had anterior capsular tags; four (0.31 percent) had a posterior capsule tear; and 25 (1.92 percent) needed their incisions done manually. There were no cases of posterior lens dislocation. "What our study and others are suggesting is that with the significant improvements in hardware and software that have occurred—and the surgeons learning more about the procedure—the femtosecond surgeon can expect a much shorter, predictable learning curve," says Dr. Roberts.

Complications in Large Femtosecond Cataract Studies

	Chee SP, et al. (n=1,105)[10]		Roberts T, et al. Group 1 (n=200)[3]		Roberts T, et al. Group 2 (n=1,300)[3]		Abell R, et al. (n=4,000)[1]	
	# eyes	%	# eyes	%	# eyes	%	# eyes	%
Anterior capsule tear	9	0.81	8	4	4	0.31	34	1.84
Suction loss	5	0.45	5	2.5	8	0.61	N/A	N/A
Posterior capsule rupture	3	0.27	7	3.5	4	0.31	8	0.43
Anterior capsule tags	N/A	N/A	21	10.5	21	1.62	30	1.62

Taking a broad view of the literature, in 2013 the Veterans Administration commissioned a task force to do a meta-analysis of the available peer-reviewed reports on femtosecond cataract surgery and then make a recommendation about whether the VA should implement it in its hospitals. The researchers whittled 468 papers down to 16 that met their validity criteria.

Though femtosecond cataract research continues to be generated by surgeons, and femtosecond technology continues to evolve, the VA researchers found femtosecond's complication rates at the time to be similar to conventional surgery. "We tried to break the adverse effects into those that you'd only encounter with laser cases, such as docking problems, and those that the two groups would have in common, such as endophthalmitis," says Ken Gleitsmann, MD, an ophthalmologist from Hilton Head Island, S.C., and one of the report's co-authors. "The docking problems did not lead to greater complications. Even in cases in which docking might have been a problem, after subsequent docking attempts the surgery would usually proceed as it did in the other uncomplicated groups. In terms of other complications, femtosecond and conventional surgery had the same adverse events and the rates of complications were comparable between the two. However, a lot of this has to do with the small size of the study groups. As femtosecond goes out into the marketplace and you have a million cases to look at, things may look a little different. Also, making things more difficult is the fact that the complication rates with conventional surgery are so low. To get something even lower than that is difficult."

Another safety parameter that is emerging is the potential reduction in ultrasound energy needed to remove the cataract when a femtosecond laser is used to segment the nucleus. In a study co-authored by Dr. Reddy, surgeons randomized patients to femtosecond cataract surgery or conventional phaco. Fifty-six eyes had the laser and 63 underwent conventional surgery. The researchers found that the mean effective phaco time was significantly lower in the laser group (5.2 ±5.7 seconds) compared to the manual (7.7 ±6 seconds; $p=0.025$). There was also a significant difference in the mean phaco energy between the groups (13.8 ±10.3 percent in laser vs. 20.3 ±8.1 percent for manual; $p<0.001$). However, the safety results of each procedure were equal, with no adverse events in either at one day postop.[9] The 4,000-eye study from Tasmania also found that effective phaco time was statistically significantly lower in laser patients, but didn't find an increased risk of complications that would be associated with this increased time.[1]

Dr. Reddy says that the exact measurement of phaco time from surgeon to surgeon, as well as its effect on out-

comes, isn't cut-and-dried, however. "I found that femtosecond cataract helped with regard to reduced effective phaco time," he says, "but, as a surgeon, I can't say there's a significant difference between the two modalities. Some doctors have a habit of continuing the energy in between one fragment to another and others don't. It's a factor that's very surgeon-dependent."

All images: Robert Rivera, MD

Many studies find the laser is adept at creating well-sized, round capsulotomies.

The Capsulotomy

One particular aspect of femtosecond cataract surgery that's gotten a lot of analysis in the literature is the creation of the capsulotomy.

No one disputes the femtosecond laser's ability to create a precise, very circular rent in the capsule, and studies have proven how accurate it can be.[4,5] Studies have even shown this may help with positioning an intraocular lens postop.[6] Controversy has begun, however, after one recent study reported laser capsulotomies may have some weak points that could lead to tearing.[7]

The tearing paper was a prospective analysis of 804 patients undergoing femtosecond cataract surgery and 822 undergoing conventional phaco. In it, the researchers found a statistically significant increased rate of anterior capsule tears in the laser group (15; 1.87 percent) when compared to the conventional group (1; 0.12 percent). In seven cases, the anterior tear extended to the posterior capsule. The researchers examined tissue samples on scanning electron microscopy and found irregularities at the margin of the capsules, as well as apparently misplaced laser pits in normal segments of the tissue.[7] The pits are described as sitting 2 to 4 µm apart at locations 10 to 100 µm radial to the capsule edge. The researchers said that, in some cases, the anterior capsulotomy integrity appeared to be compromised by "postage-stamp" perforations and aberrant laser pulses that may occur due to patient eye movement. They also acknowledged, however, that the surgeon learning curve may be to blame for some of the increased complication rates with the laser procedure.

Dr. Roberts says rates such as these may be outliers, and haven't been his experience. "We published our safety study of 1,500 patients two years ago and a follow-up study of another 3,000 patients is in press," he says. "Our anterior capsular tear rate is 0.2 percent now. Other papers, such as that by Julian Stevens at Moorfields which had 0.1 percent, aren't finding a high rate such as this."

Hyderabad's Dr. Reddy says he was involved in an animal model study with Heidelberg, Germany's, Gerd Auffarth, MD, where they specifically looked at capsulotomy strength in porcine corneas. "We stretched capsulotomies created manually and by a laser," he says. "The study showed the laser capsulotomies were as good, if not better, than manual ones. Also, if the laser edge is weak from a clinical point of view, then there should be tears in every case, because as we operate we're pulling fragments through that capsulotomy and we catch the edge as we do it, but there aren't."

In the study from Moorfields, surgeons retrospectively reviewed 1,000 laser capsulotomies performed over a period of about a year. They found complete 360-degree capsulotomies in 998 cases (99.8 percent).[8] In the two incomplete capsulotomies, one was due to the laser activation having to be aborted, and the second had a tissue tag that became a tear, leading to a 0.1-percent rate of tearing.[2]

Dr. Reddy adds that there are certain patients with an unusual capsule/zonule configuration who will be easier to operate on using a femtosecond laser, and where the laser capsulotomy would be preferable. "Whenever the anterior zonules are inserting into the anterior capsule, there are some aberrations in some patients," Dr. Reddy explains. "Some of them get inserted a little more proximal toward the center. So, when you try to do a manual capsulorhexis, these fibers will catch it and from then on, it will be a struggle for the surgeon. But when you do a laser capsulotomy, it cuts all these microscopic fibers, so you'll never have that problem."

Visual Results

In terms of refractive results, published studies show femtosecond and conventional surgery both produce very good outcomes.

"As to whether there's a difference in visual outcomes between conventional and femtosecond cataract surgery, the short answer from our report is no," says Dr. Gleitsmann. "Of the studies we looked at, and translating all acuities into decimal equivalents, the visual outcomes were no different between those two groups. To make a long story short, the outcomes are so good for conventional surgery that it's pretty hard to improve on them. Also, the numbers themselves for visual acuity are actually kind of rough. For instance, if someone says, 'My results are 20/20,' and someone else says, 'Mine are 20/18,' it really isn't clinically significant."

A study from Singapore that's currently in press, however, has found that femtosecond cataract surgery produced better visual outcomes on some measurements when compared to 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.

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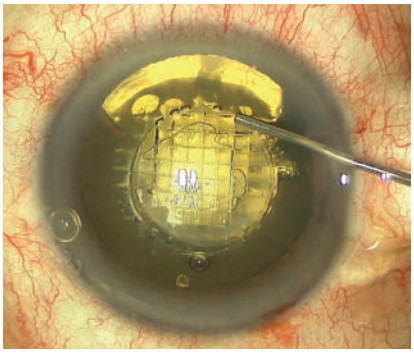
random sample of conventional phaco cases. In the study, 18 surgeons performed femtosecond cataract surgery with the Victus laser (Bausch + Lomb) on 1,105 eyes of 803 patients. They then compared the visual outcomes of 794 laser cases to 420 controls. The investigators found that the percentage of patients who saw 20/25 or better uncorrected at six weeks was 68.6 percent in the study group vs. 56.3 percent of the controls ($p<0.0001$). The manifest refraction spherical equivalent was also statistically significantly lower in the laser group (-0.08 ±0.36 D compared to -0.13 ±0.4 D; $p=0.034$). The mean absolute error, however (0.30 ±0.25 D for the laser vs. 0.33 ±0.25; $p=0.062$) and the mean square error (0.16 ±0.27 D vs. 0.17 ±0.28 D) were similar. The researchers say the complication rate was low.[10]

A group from Europe performed a prospective, randomized study of the effects on surgically induced astigmatism of a laser-created entry wound vs. a manual one, since induced astigmatism could affect postop vision. They performed a 2.8-mm clear corneal incision in 20 eyes of 20 patients using a disposable keratome and a 2.8-mm, biplanar clear corneal tunnel in 20 eyes of 20 patients using a femtosecond laser. They found no significant difference in SIA (0.47 ±0.13 D for the laser vs. 0.41 ±0.14 D for the manual incisions; $p=0.218$), or any difference in induced higher-order aberrations. However, the axis deviation from the planned axis was significantly smaller in the laser group (4.47 ±2.59 degrees vs. 7.38 ±4.72 degrees; $p=0.048$).[11]

Challenging Cases

Though there haven't been studies specifically designed to analyze femtosecond cataract surgery in difficult cases (such as pseudoexfoliation or patients with brunescent lenses), the gestalt that has emerged from the literature is that the laser may put less stress on ocular structures.[12]



Pre-segmenting a nucleus can help reduce the duration of phaco time.

"In our paper, complications didn't arise in any of these complex cases,"[3] says Dr. Roberts. "In fact, we have found that the laser is particularly beneficial in these cases as the capsulotomy is consistently round and intact, eliminating the risk of the manual capsulotomy tearing out when the zonules are weak. Also, a pre-fragmented nucleus allows you to do much less manipulation in the bag—with lower phaco power and time—reducing the risk of zonular dialysis."

Research shows, however, that surgeons may have to exercise care when using the femtosecond laser for cataract surgery in patients sensitive to intraocular pressure changes, due to the increase in intraocular pressure that occurs during the suction during preop laser docking. A prospective study from Hong Kong used a handheld applanation tonometer to measure intraocular pressure during femtosecond cataract surgery with the Victus in 41 eyes of 35 patients. The mean IOP went from 17.2 mmHg pre-suction to 42.1 mmHg during suction, then back down to 13.8 mmHg after suction. The mean suction duration was 216 seconds. They found the increase was statistically significant compared to pre-suction levels (25 ±11.3 mmHg; $p<0.01$), and concluded that surgeons should proceed with caution in patients with ocular conditions that are vulnerable to IOP fluctuations.[13]

Though there is currently a lot of equivalence between laser cataract surgery and conventional phaco in the literature, Dr. Roberts says he expects laser technology to improve. "At a recent Academy meeting, I went to a review of corneal laser surgery," he says. "During the session, an interesting comment was made that it's taken many years and many major upgrades to both hardware and software to get where we currently are in terms of the powerful lasers used for corneal grafts and refractive procedures. So, the question becomes: Is the current evidence-based literature what one would expect for laser cataract surgery as a new and evolving technology that has the potential to make surgery more accurate, safer and predictable? I'd argue that it is." REVIEW

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Classic beta blocker adjunctive therapy for the right patient at the right time[3]

The concomitant use of two topical beta-adrenergic blocking agents is not recommended[4,5]

Indications and Usage

ISTALOL® (timolol maleate ophthalmic solution) is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. It may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

Important Safety Information for Istalol® and Timoptic® in Ocudose®

- Both ISTALOL® (timolol maleate ophthalmic solution) and TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) are contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of the product.
- **The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory reactions and cardiac reaction, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.**
- Patients with a history of atopy or severe anaphylactic reactions to a variety of allergens may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.
- Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.
- Beta-adrenergic blocking agents may mask signs and symptoms of acute hypoglycemia or certain clinical signs of hyperthyroidism. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving either insulin or oral hypoglycemic agents, or patients suspected of developing thyrotoxicosis, should be managed carefully, with caution.
- In patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta adrenergic receptor blocking agents because these agents impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli.
- The most frequently reported adverse reactions have been burning and stinging upon instillation. This was seen in 38% of patients treated with ISTALOL and in approximately one in eight patients treated with TIMOPTIC in OCUDOSE. Additional reactions reported with ISTALOL at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity.

Please see Brief Summary of Prescribing Information for ISTALOL and TIMOPTIC in OCUDOSE on the following pages.

For the patients who need incremental IOP reduction in a preservative free form[6]

Preservative-Free

TIMOPTIC® in OCUDOSE®
(TIMOLOL MALEATE 0.5% OPHTHALMIC SOLUTION) (DISPENSER)

For the patients who need incremental IOP reduction in a once a day form[6]

Istalol®
(timolol maleate ophthalmic solution) 0.5%

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US/TOP/14/0017(1)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use TIMOPTIC® 0.25% AND 0.5% (timolol maleate ophthalmic solution) in OCUDOSE® (DISPENSER) safely and effectively. See full prescribing information for TIMOPTIC in OCUDOSE.

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION
in a Sterile Ophthalmic Unit Dose Dispenser

TIMOPTIC® 0.25% AND 0.5% (TIMOLOL MALEATE OPHTHALMIC SOLUTION)

in OCUDOSE® (DISPENSER)

INDICATIONS AND USAGE

Preservative-free TIMOPTIC in OCUDOSE is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC in OCUDOSE may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

CONTRAINDICATIONS

Preservative-free TIMOPTIC in OCUDOSE is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Preservative-free TIMOPTIC in OCUDOSE should be discontinued.

Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which TIMOPTIC in OCUDOSE is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including Preservativefree TIMOPTIC in OCUDOSE.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

General: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Preservative-free TIMOPTIC in OCUDOSE, alternative therapy should be considered.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. TIMOPTIC in OCUDOSE should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients: Patients should be instructed about the use of Preservative-free TIMOPTIC in OCUDOSE.

Since sterility cannot be maintained after the individual unit is opened, patients should be instructed to use the product immediately after opening, and to discard the individual unit and any remaining contents immediately after use.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Drug Interactions: Although TIMOPTIC (timolol maleate ophthalmic solution) used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC (timolol maleate ophthalmic solution) and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Preservative-free TIMOPTIC in OCUDOSE should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Preservative-free TIMOPTIC in OCUDOSE, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: (See PRECAUTIONS, *General*, *Anaphylaxis*)

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000 times, respectively, the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: *Teratogenic Effects* — Pregnancy Category C. Teratogenicity studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

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

Nursing Mothers: Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.
CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.
DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.
IMMUNOLOGIC: Systemic lupus erythematosus.
NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.
SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.
HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.
RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.
ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).
SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*); and tinnitus.
UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta blocking agents, and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura; agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with Ophthalmic Solution TIMOPTIC (timolol maleate ophthalmic solution) resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Overdosage has been reported with Tablets BLOCADREN* (timolol maleate tablets). A 30 year old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

Preservative-free TIMOPTIC in OCUDOSE is a sterile solution that does not contain a preservative. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be guaranteed after the individual unit is opened, the remaining contents should be discarded immediately after administration.

Preservative-free TIMOPTIC in OCUDOSE is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent Preservative-free TIMOPTIC in OCUDOSE in the affected eye(s) administered twice a day. Apply enough gentle pressure on the individual container to obtain a single drop of solution. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) administered twice a day.

Since in some patients the pressure-lowering response to Preservative-free TIMOPTIC in OCUDOSE may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with Preservative-free TIMOPTIC in OCUDOSE.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of 0.5 percent TIMOPTIC (timolol maleate ophthalmic solution) twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted taking into consideration that the preparation(s) used concomitantly may contain one or more preservatives. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, *Drug Interactions, Beta-adrenergic blocking agents.*)

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Lawrenceville
NJ 08648
USA

By: Laboratories Merck Sharp & Dohme-Chibret
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Based on PI - 514266Z/069A-03/09/9689-9690
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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ISTALOL® (timolol maleate ophthalmic solution) 0.5% safely and effectively. See full prescribing information for ISTALOL.

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

Istalol (timolol maleate ophthalmic solution) 0.5% is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

4.1 Asthma, COPD: Istalol is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease (see **WARNINGS AND PRECAUTIONS, 5.1, 5.3**).

4.2 Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock: Istalol is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure (see **WARNINGS AND PRECAUTIONS, 5.2**); cardiogenic shock.

4.3 Hypersensitivity Reactions: Istalol is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this product in the past.

WARNINGS AND PRECAUTIONS

5.1 Potentiation of Respiratory Reactions Including Asthma: Istalol contains timolol maleate; and although administered topically, it can be absorbed systemically. Therefore, the same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see **CONTRAINDICATIONS, 4.1**).

5.2 Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Istalol should be discontinued (see also **CONTRAINDICATIONS, 4.2**).

5.3 Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease [other than bronchial asthma or a history of bronchial asthma in which Istalol is contraindicated (see **CONTRAINDICATIONS, 4.2**)] should, in general, not receive beta-blocking agents, including Istalol.

5.4 Increased Reactivity to Allergens: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

5.5 Potentiation of Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

5.6 Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

5.7 Masking of Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

5.8 Contamination of Topical Ophthalmic Products After Use: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PATIENT COUNSELING INFORMATION, 17**).

5.9 Impairment of Beta-adrenergically Mediated Reflexes During Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

5.10 Angle-Closure Glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This may require constricting the pupil. Timolol maleate has little or no effect on the pupil. Istalol should not be used alone in the treatment of angle-closure glaucoma.

5.11 Cerebrovascular Insufficiency: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Istalol, alternative therapy should be considered.

5.12 Choroidal Detachment: Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

ADVERSE REACTIONS

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

The most frequently reported adverse reactions have been burning and stinging upon instillation in 38% of patients treated with Istalol. Additional reactions reported with Istalol at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity. The following additional adverse reactions have been reported less frequently with ocular administration of this or other timolol maleate formulations.

Timolol (Ocular Administration): *Body as a whole:* Asthenia/fatigue and chest pain; *Cardiovascular:* Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon and cold hands and feet; *Digestive:* Nausea, diarrhea, dyspepsia, anorexia, and dry mouth; *Immunologic:* Systemic lupus erythematosus; *Nervous System/Psychiatric:* Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness and memory loss; *Skin:* Alopecia and psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash; *Respiratory:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections; *Endocrine:* Masked symptoms of hypoglycemia in diabetic patients (see **WARNINGS AND PRECAUTIONS, 5.6**); *Special Senses:* Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis, decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see **WARNINGS AND PRECAUTIONS, 5.12**); *Urogenital:* Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

6.2 Postmarketing Experience

Oral Timolol/Oral Beta-blockers: The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

DRUG INTERACTIONS

7.1 Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and Istalol® should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

7.2 Calcium Antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents, such as Istalol, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

7.3 Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

7.4 Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

7.5 CYP2D6 Inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine) and timolol.

7.6 Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C: Teratogenicity studies have been performed in animals. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. Istalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers: Timolol has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Istalol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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

OVERDOSAGE

There have been reports of inadvertent overdosage with Istalol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose. In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin. Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test. Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

PATIENT COUNSELING INFORMATION

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (see **CONTRAINDICATIONS, 4.1, 4.2**) Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (see **WARNINGS AND PRECAUTIONS 5.8**) Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart. Patients should be advised that Istalol® contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following Istalol® administration.

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New Technology Gains Momentum

Walter Bethke, Managing Editor

Femtosecond lasers and intraoperative aberrometry intrigue surgeons.

New technology for cataract surgery appears to be the proverbial snowball rolling downhill—it continues to gradually grow in size in terms of users on our annual survey of cataract surgeons. Femtosecond cataract and, to a lesser extent, intraoperative wavefront aberrometry, have both garnered new converts over the past year, and some indicators on the survey point toward more adherents in the future.

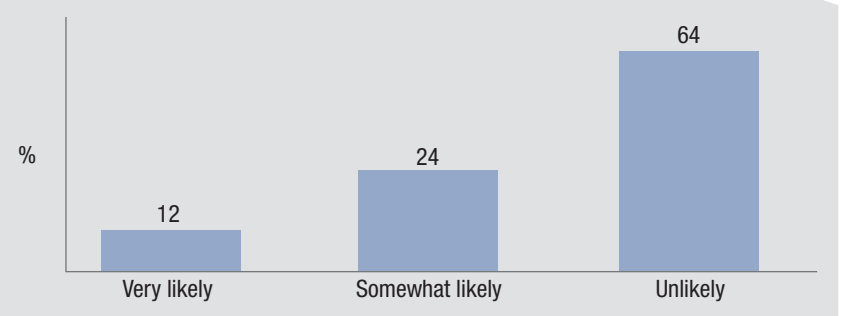
These are a couple of the revelations in this month's survey of surgeons about their cataract techniques. The e-mail survey was opened by 1,742 of 11,600 subscribers to *Review*'s electronic mail service (15 percent open rate) and 181 filled in their answers. To see how your cataract technique compares to the surgeons on the survey, read on.

Burgeoning Technology

Cataract surgeons seem to be warming up to the idea of femtosecond cataract, with the percentage saying they use it for some aspect of cataract surgery growing from 23 percent on last year's survey to 31 percent this year. The steps the laser is used for most often are the capsulotomy (91 percent of respondents) and nuclear fragmentation (91 percent). The percentage who say they use it for the entry and paracentesis incisions actually decreased from last year, however. Last year, 64 percent used it for the entry wound and 55 percent used it for the paracentesis, compared to just 38 percent and 29 percent, respectively, this year. The full results appear in the graph on p. 46.

The surgeons who currently use the technology appreciate many of the

Likelihood of Performing Femto Cataract Surgery Within a Year



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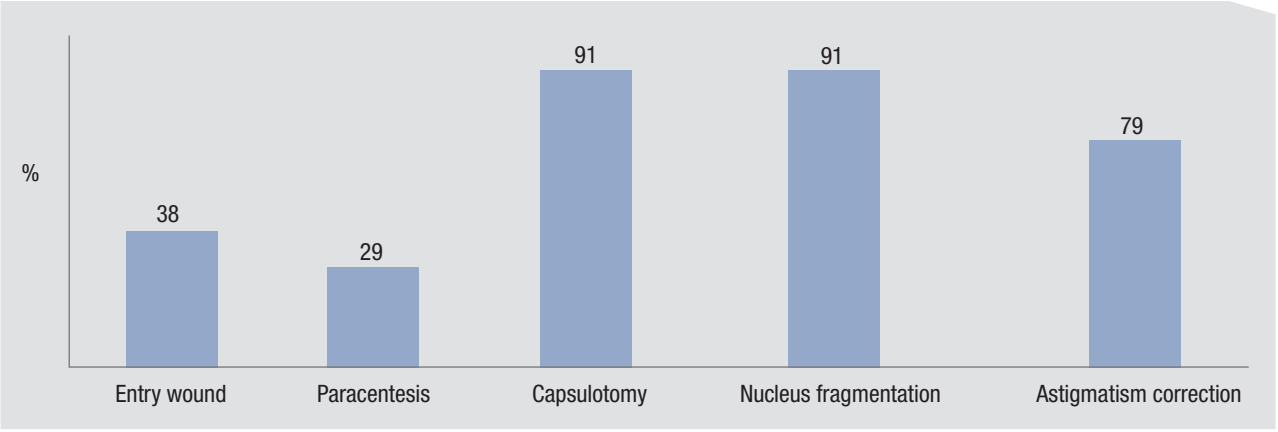

things it does for them, but note that it's not perfect. John Sheppard, MD, of Norfolk, Va., is one of these physicians. "I enjoy the procedure," he says. "It's an excellent marketing tool, and has outstanding advantages for capsulorhexis and LRIs. I'm enjoying newer nucleus fragmentation techniques like the 'ice cube.' The paracentesis and primary incisions don't yet have a clear-cut advantage, though. It's still costly, but our fastest growing single segment of premium surgery is the LenSx." Jeffersonville, Ind., surgeon Curtis Jordan says, "It makes a great rhexis, nucleus division and astigmatic keratotomy, but the temporal wound is too far anterior, so I make my own temporal wounds and paracenteses." A surgeon from California chooses to make mostly AK cuts with the femtosecond. "I like that it makes all the cuts," he says. "The bubbles [created during laser operation] can block the view, but I do like the pneumodissection. I don't like the entry incisions made by it. Also, the suction can break vessels and make the eye very irritated; the eye looks less traumatized after regular cataract extraction. I like making AK incisions with it, primarily." A Texas surgeon also gives it mixed reviews. "I like that it makes for a very standardized procedure," he says. "I don't like that cortical cleanup is much more difficult with it, but using a bimanual approach simplifies things."

Looking ahead, 12 percent of the surgeons say they're very likely to perform femtosecond cataract surgery in the next year, and 24 percent say they're somewhat likely to do so. The main reasons given are, "it's the future," or "patient demand." On the other hand, 64 percent say they're unlikely to do it, though this percentage is down from last survey's 73 percent. The main reason given by many of the uninterested surgeons is the cost/benefit ratio. "It works OK but is too cumbersome to align the patient," says an Ohio surgeon who tried the technology but is unlikely to go back to it. "There's too much of a reliance on the technician, too many extra steps where things can go wrong or out of your control, it takes too long and is expensive without any clear advantage to the patient. The technology is not currently advanced enough to be worth the hassle."

Richard Erdey, MD, of Columbus, Ohio, also says he's unlikely to use femtosecond for his cataract surgeries. "There's no peer-reviewed paper demonstrating any advantage of it versus a very efficient two-handed phaco chop technique," he avers. "There's also no peer-reviewed report demonstrating the long-term predictability and stability of vertical corneal incisions made with the femto versus those made with steel or diamond blades. I prefer lamellar AK techniques such as bilateral clear cornea incisions. I like scleral tunnel on the steep, with-the-rule axis (scleral recession) and LVC when a toric IOL isn't indicated or is unaffordable." Douglas Liva, MD, from Ridgewood, N.J., is also looking for a better value considering the cost involved. "I'm unlikely to use it because of cost and the fact that there's no real data showing it to be better or safer," he says. "In fact, it seems to have more complications and take longer. I'm also not comfortable with the ethics in its presentation to the patient since it's sold as an uncovered service as it is used to correct astigmatism. What do you tell the patient who wants it and has no significant astigmatism?" George Walters, MD, of Del Rio, Texas, says he's also unlikely to start doing it. "It's too costly and doesn't eliminate the need for manual intraocular manipulation," he says. "It doesn't eliminate complications during phaco, cortical cleanup or IOL placement. It's like killing a fly with a military drone."

The other technology in contention for cataract surgeons' attention is intraoperative wavefront aberrometry. Twelve percent of the surgeons say they use it, which is up slightly from last year's 9 percent, and 34 percent say they're either very likely or somewhat likely to use it in the coming year,

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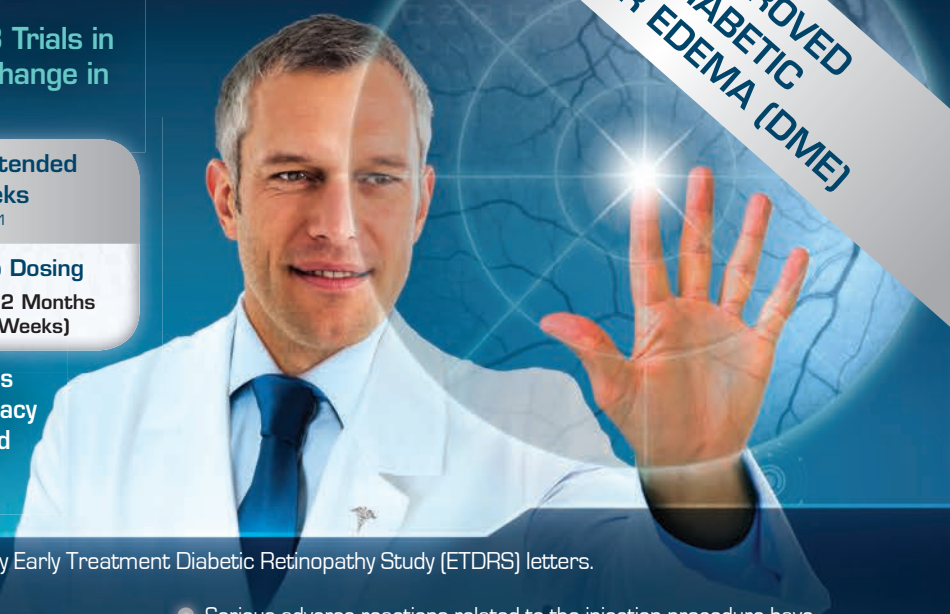

*BCVA = best-corrected visual acuity, as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

IMPORTANT SAFETY INFORMATION FOR EYLEA® (aflibercept) INJECTION

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

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

For more information, visit www.EYLEA.com.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. October 2014.

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

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

10/2014
LEA-0624

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation

5 WARNINGS AND PRECAUTIONS

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

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

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

6 ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Adverse Reactions	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%
Eye pain	9%	6%
Cataract	8%	9%
Vitreous floaters	6%	3%
Corneal erosion	5%	3%
Intraocular pressure increased	5%	3%
Conjunctival hyperemia	5%	6%
Vitreous detachment	3%	3%
Foreign body sensation in eyes	3%	3%
Lacrimation increased	3%	2%
Vision blurred	2%	2%
Intraocular inflammation	2%	<1%
Injection site pain	2%	<1%

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

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

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-52 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

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

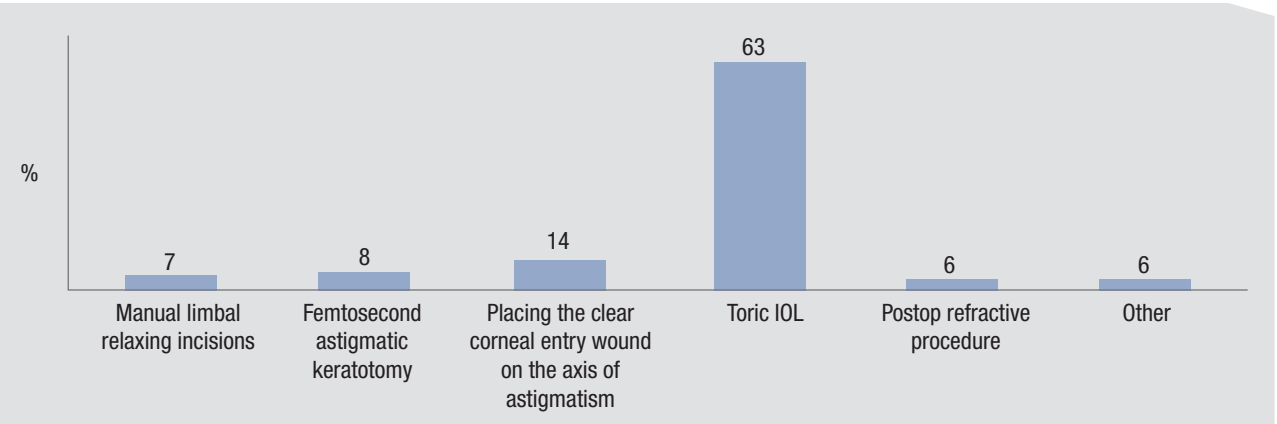
U.S. License Number 1760

Issue Date: October 2014
Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents

LEA-0618

Preferred Method for Managing Pre-existing Astigmatism in a Cataract Patient



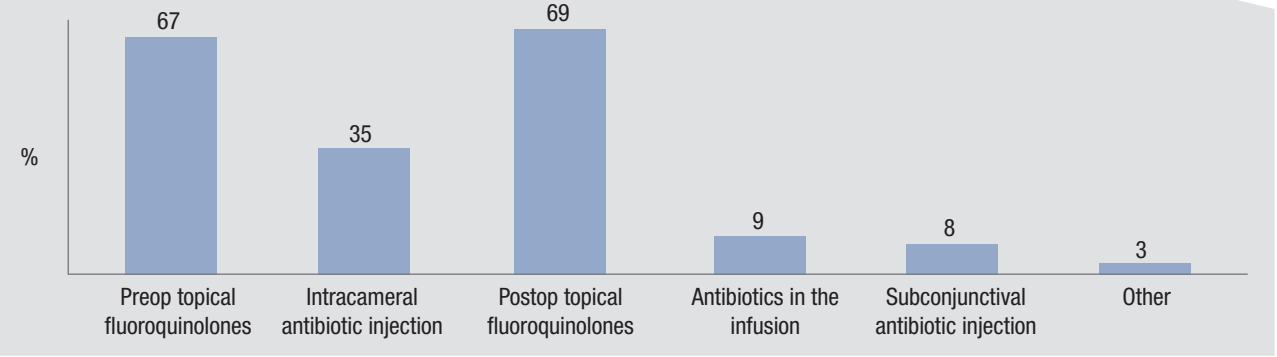
which is an increase over last year's 26 percent. However, this means 88 percent of the respondents don't use it, and two-thirds say they're unlikely to using doing it this year.

Sacramento, Calif., surgeon Richard Meister says he appreciates the technology. "It yields good readings on post-refractive patients and those that we can't do the IOLMaster on," he says. "It's good for acquiring the astigmatism and the axis." Robert Lehmann, MD, of Nacogdoches, Texas, also feels it helps him in the OR. "My outcomes are closer to the target," he says. "I'm also able to adjust the cylinder and the toric IOL position at the expense of a little extra time and cost." Another surgeon from Texas warns that it might not be perfect for all cases, though, when he says, "It's sometimes finicky for low-power toric IOL alignments." A New York surgeon thinks it comes in handy for patients who are usually difficult to pin down on biometry. "It gives me an accurate intraocular lens measurement in the post-LASIK patient," he says. Nick Mamalis, MD, of Salt Lake City, however, thinks the technology plays a key role in some cases. "It's essential to have this technology for patients who have had previous refractive surgery and/or have astigmatism," he says, "especially with toric IOLs."

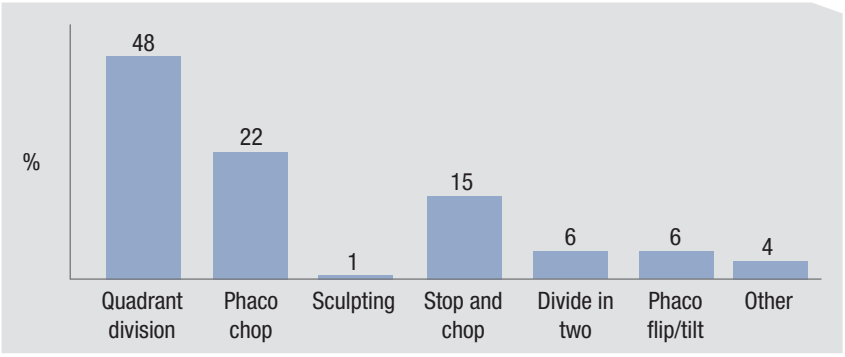
Many of the 88 percent who don't use intraoperative aberrometry say that they're concerned it will slow them down during surgery without giving them a commensurate benefit. Will Sawyer, DO, of New Braunfels, Texas, says, "The benefit is the ability to recheck your IOL calculations intraoperatively. The cons are cost, the time spent in surgery and the fact there's not a 100-percent guarantee that the residual refractive error will be gone." A surgeon from Nashville says he isn't yet convinced. "My IOL predictions are sufficient, and studies have not yet shown significant result changes of greater than 1 D on a regular basis," he says. "I don't use it at this time. A true drawback would be that these lenses have to be ordered ahead of time. How do I know that my surgery center is going to have what I need at all times?"

A California surgeon is open to using the technology down the road. "It's about affordability," he says. "Someone has to fund the new technologies, so if the patients will pay for it—i.e., if enough of my practice's patients will monetarily endorse intraoperative aberrometry—then we will invest in it."

Steps Taken to Avoid Infection (in Addition to Iodine)



Preferred Phacoemulsification Technique



Managing Astigmatism

Surgeons also weighed in on their usual method for treating pre-existing astigmatism in their cataract patients.

The most popular option is a toric IOL, chosen by 63 percent of the respondents. In second-place is the practice of putting the entry wound on the steep axis (14 percent). "The toric IOL works reasonably well, is easy to implant and is profitable," says New Jersey's Dr. Liva. "The toric lens is a perfect example of capitalism working well: The industry benefits with increased profits for research, the physician benefits with increased reimbursement to compensate for the unfairly low cataract surgery compensation and the patient benefits with improved uncorrected vision without significant risk. It's a triple win." A Texas surgeon says that in most cases he uses the placement of the entry wound to control the cylinder. "I like to go on-axis for low-power cylinder," he says. "Anything greater will require an additional AK or a toric lens. I like to reduce the power requirement of the toric IOL by operating on-axis."

Phaco Technique

In terms of breaking up the cataractous lens, the most popular option on the survey is quadrant division, chosen by 48 percent of respondents.

"Quadrant division gives me the best in-the-bag control, away from the cornea," says Francisco Tellez, MD, of Wyomissing, Pa. "Also, this is the procedure I initially trained with and is the one with which I am most comfortable." Steven Stiles, MD, of Tarzana, Calif., prefers quadrant division because of its effect on the lens. "With it, the nucleus spins," he says, "and it's easy to make four grooves and use a splitter to create four pieces which are easily grasped with aspiration and pulled to the center for easy removal." A surgeon from Marion, Ohio, Filmore A. Riego, thinks quadrant division is a good all-around technique for different patient presentations. "Most cataracts are best removed using this technique," he says.

As for other techniques, 22 percent prefer phaco chop and 15 percent do stop-and-chop. Bettendorf, Iowa, surgeon Lisa Arbisser, explains why she prefers phaco chop: "The size of the rhexis is always tailored to the optic, not to the nucleus," she says. "With vertical chop one stays in view within the rhexis and only requires a 5- to 6-mm pupil. One is never pushing on subincisional zonules. It's the most ultrasound-sparing technique. One can adjust the number of sections split based on lens density so there is never a large chunk brought near endothelium. The posterior capsule is protected by the remaining nuclear sections in the bag until the last fragment is removed."

A String of Pearls

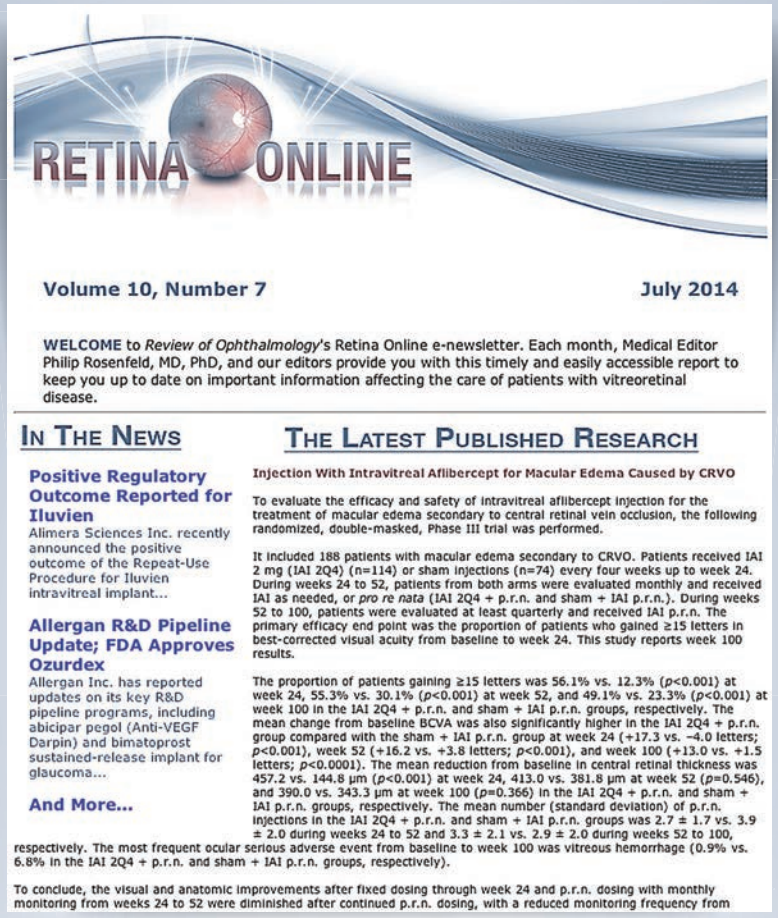
Surgeons also took the time to share their favorite surgical techniques.

Kevin Dinowitz, MD, of Bloomfield, Conn., says to pay attention to the use of your viscoelastic. "I find it better to leave the viscoelastic under the toric IOL and not remove it as stated in the normal convention," he says. "When it's removed, the IOL actually is more likely to spin and move out of position." Virginia's Dr. Sheppard provides both conventional and femtosecond cataract advice: Use the primary blade to make the initial nick in the anterior capsule," he says. "For femtosecond, be sure to complete your hydrodissection; it makes subincisional cortex removal much easier, and it's much safer now, with smaller bubbles created by the lower laser energy and shorter treatment times."

Ohio's Dr. Erdey likes a scleral recession technique. "I perform scleral recession—a scleral tunnel placed on the steep corneal meridian with its length titrated to astigmatism magnitude—as a long-term, stable, reversible technique for correction of with-the-rule cylinder less than 2.5 D," he explains. "I routinely perform scleral recession when a patient can't afford a toric IOL or when it's indicated because of mild corneal asymmetry or warpage." Dr. Riego modifies his capsulorhexis for certain cases. "I make a bigger capsulorhexis for diabetics with retinopathy," he says, "or for diabetics who are most likely going to develop retinopathy. I use it also for high myopes." Thomas Castillo, DO, from Beaver Dam, Wis., says it pays to hit the film room. "Record every case," he says. "You never know what you may learn by watching an instance when things don't go perfectly."

Ligaya Prystowsky, MD, of Nutley, N.J., shares a sentiment that most surgeons adhere to in the operating room and the clinic: "There's always room for improvement." REVIEW

RETINA ONLINE
E-NEWSLETTER



RETINA ONLINE

Volume 10, Number 7 July 2014

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

IN THE NEWS

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

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

And More...

THE LATEST PUBLISHED RESEARCH

Injection With Intravitreal Aflibercept for Macular Edema Caused by CRVO

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

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

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

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

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.

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REVIEW® of Ophthalmology

Is There a Place for PAs in Ophthalmology?

Michelle Stephenson, Contributing Editor

Few ophthalmology practices employ PAs, and those that do typically use them for primary care.

Although physician assistants have been used successfully as physician extenders in primary care and in some subspecialties, they have rarely infiltrated ophthalmology practices. Even when they are employed by ophthalmology practices, they are rarely practicing eye care.

According to the American Academy of Physician Assistants, there are only approximately 70 PAs currently working in ophthalmology practices. One reason for this low number is that PA students receive very little, if any, training in eye care. Two of these 70 PAs are employed by Minnesota Eye Consultants, and their main roles are performing preop-

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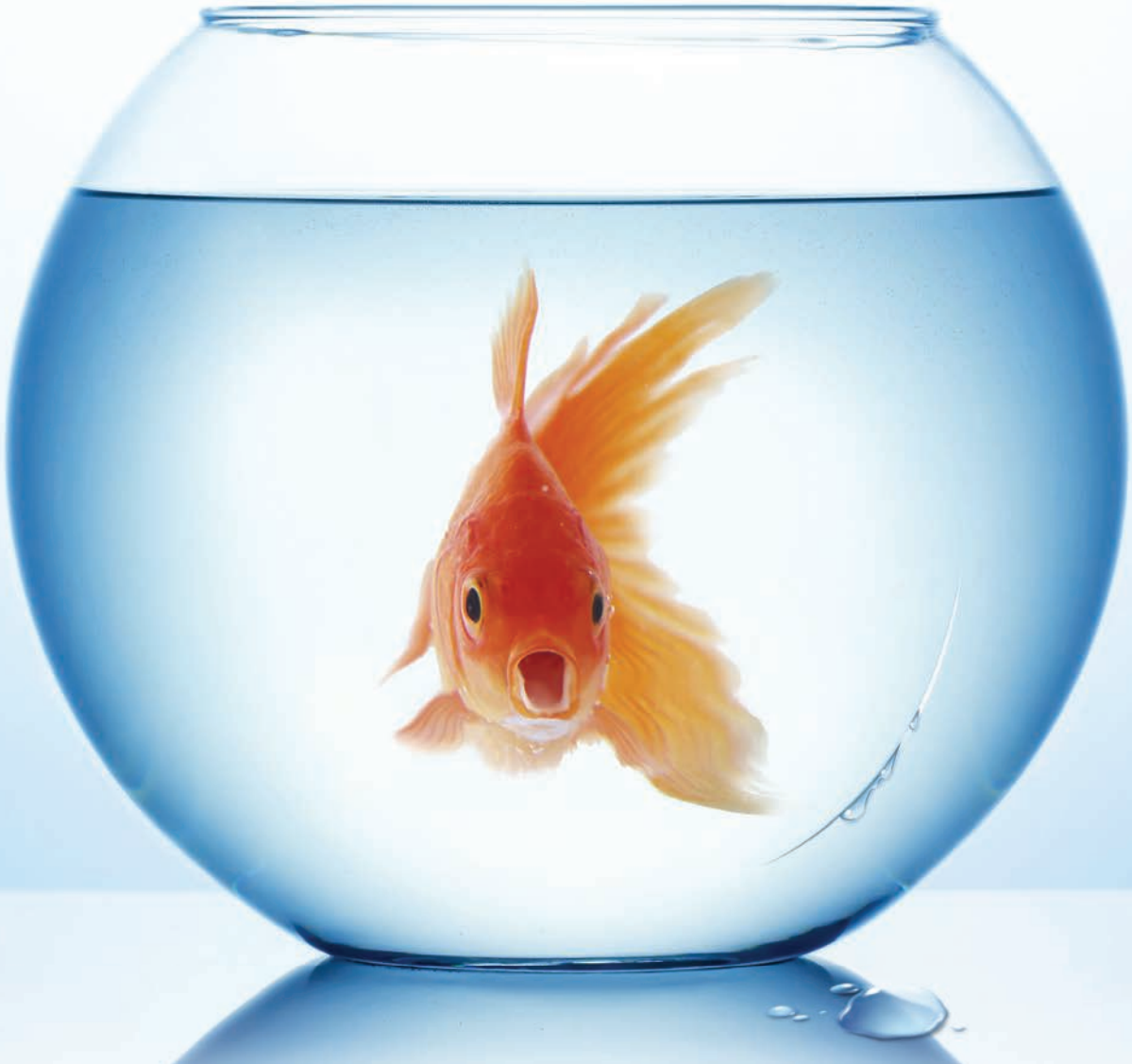

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erative histories and physicals for patients who are scheduled to undergo surgery and providing urgent-care services to employees. In the past year, they have also started to perform some autoimmune screening.

"Before any type of significant surgery, a patient is required to have a preoperative history and a physical to assess the risk of the anesthesia and to determine whether or not they are healthy enough to proceed with the surgery. Only physicians, physician assistants and nurse practitioners can perform these physicals," says Laura C. Gundale, PA-C, one of the PAs at Minnesota Eye Consultants.

It is ideal for patients to be able to have their physicals performed at the ophthalmologists' office rather than trying to schedule an appointment with their primary-care providers. "It simplifies things for our patients," says Ms. Gundale. "If they go to their primary-care doctor to have their physicals, sometimes they can't get in during the appropriate time period. Another problem that can arise is if a patient forgets to bring along our paperwork, the primary-care physician doesn't know our practice's guidelines, but if patients get their physicals done here, then it's all pretty streamlined."

Another benefit is ease of scheduling. According to Ms. Gundale, the physical must be done within 30 days of surgery. "Often, if a patient is having cataract surgery, we'll do one eye and then the other eye two weeks later, so it does require some negotiating with the schedule," she says. "Typically, I will do the physical a few days before the first procedure. For simple laser procedures, we do some of the physicals the same day as the procedure. For more complicated patients who have more complicated surgeries, I like to request records from their primary-care physician or their cardiologist. Part of the reason that we like to do it ahead of time is to make sure we have all of the information we need. If I am concerned that a patient is not optimized for surgery, I will refer him to his primary-care physician or cardiologist to get that clearance, but the majority of the time, that isn't necessary."

A few practices are using PAs for eye care, and Ms. Gundale notes that there are some areas into which PAs could easily expand their scope of practice. "A lot of our patients are seen for dry eye, which can be caused by allergies," she says. "We

often send patients to their primary-care doctor or to an allergist to get testing done. We would like to find a way for the PAs here to perform that testing to keep everything in-house and a little bit more streamlined for the patient. PAs are also testing for Sjögren's syndrome, and we do a blood panel for patients who have significant dry eye and other systemic symptoms."

In these cases, the ODs and MDs in the practice refer patients to one of the PAs, who does a brief history and physical and runs the blood panel. "If anything comes back positive, we send a letter back to the referring provider and typically refer the patient to rheumatology," says Ms. Gundale. "Those are a few areas where we are extending our services. We have a large practice that includes ODs and MDs, so for routine eye care, I think the ODs are the more appropriate providers."

Worth the Training and Money?

John Sheppard, MD, in practice at Virginia Eye Consultants, believes that ODs are the preferred physician extenders for ophthalmology practices. He has employed PAs in the past, but says that it wasn't an optimized experience. "In some of the other medical fields, the skills that the PA can extend are not as highly specialized as the skills we need in ophthalmology," says Dr. Sheppard. "The ideal clinical physician extender in ophthalmology is either a really good tech or an optometrist. The whole philosophy of physician extenders in ophthalmology is to allow the doctor to do what the doctor does best. That, of course, is the diagnosis of the condition and the recommendation for treatment and surgery. An optometrist can help with that, except in terms of the procedural surgical decision. In a routine case, the surgical decision is pretty straightforward, too, like a symptomatic cataract, and extenders can make that call reliably. That frees up the ophthalmologist to perform more surgery."

He adds that a few select practices allow PAs to assist with the actual surgery. "The PAs in some of those practices will actually make the incision, and that includes the corneal incision and the capsulorhexis," he says. "That's pretty outrageous, but that's what happens every day in cardiac surgery. The PAs are so highly trained that they will crack the chest,

position the chest expander and harvest the vein. Then, the cardiovascular surgeon actually performs the coronary anastomosis."

Dr. Sheppard notes that the PA in his office just didn't have enough to do. Additionally, she was not trained in ophthalmology, and training her just didn't make sense. "She was sitting around all of the time, and there wasn't that much for her to do," he says. "Then, we tried to use the PA to help run clinical research for us. The problem with that was that the PA needed to have not only documentation skills, but also skills in ophthalmic examination, like running all of the diagnostic devices. A PA isn't trained in that. We would have had to train our PA just like we do our technicians. PAs have a highly competitive graduate degree, and they were taking the same orientation course to push the buttons for the visual field and OCT machines as these technicians who are fresh out of college and have far fewer qualifications than PAs do. Why would I pay a PA three times more than my technician staff to push the button on the field machine and the OCT?"

His practice finds it more useful to have subspecialized optometrists. "PAs are wonderful. They just don't ideally fill in any of the gaps in an ophthalmology practice," he says. "They can treat glaucoma and dry eye, but I think that's better suited to an optometrist. It's tough to bill an ophthalmic code for a PA. You can certainly do that, but they don't have enough ocular training to make those judgments. We are working very well with optometrists who subspecialize in our practice. We have optometrists who work with a retina doc, review the OCTs and the symptoms and decide whether or not the patient needs to have an injection. Then, the retina specialists only see the patients who need an injection, or laser or surgery. That increases the morbidity level of the average patient seeing the retina doctor, better utilizing his skills. The same thing goes for glaucoma. Our optometrist who has additional expertise in glaucoma will see patients postoperatively, and if everything is fine, patients will return in a week or two. Similarly, in a routine glaucoma checkup, if the field is fine, the OCT is fine, the pressure is fine, there is no toxicity to the medicines and there is no ocular surface disease, then we will see patients in three to six months. There is no surgical decision, no need for a laser or cataract operation. We find it useful to have subspecialized optometrists who are very adept at evaluating patients for our most common procedure, which is cataract surgery, and selecting those patients for premium cataract surgery. A PA just doesn't have that background. You can bring her up to the level of a good tech, but they cost more. You can't bring her up to the level of an optometrist who has had at least five years of formal training, plus hands-on training in the practice, which is a much better head start than a PA would ever have."

However, he says that if there was an eye-specific PA program curriculum like those seen in orthopedics, cardiovascular surgery or OB/GYN, where PAs have additional training with hands-on diagnostics, therapeutics and eye care, then that would all change. "But, that has to be done now in-house, and it's just not worth it to us at that salary level," he says.

David Hardten, MD, in practice with Ms. Gundale at Minnesota Eye Consultants, agrees. "In our practice, optometrists do most of the eye-care-related work that I have heard that some practices might hire a PA to do," says Dr. Hardten. Our PAs are mostly responsible for preoperative physical exams for patients who are undergoing a procedure in the surgical center. They also do some care for our employees, because then they can be seen in our offices, and they don't have to go out and take as much time off from work, and it facilitates efficient scheduling. This makes our practice more efficient, but PAs are primarily for doing preop physicals for those having cataract surgery."

While he believes that PAs could be trained to do slit lamps and glaucoma checks and to treat conjunctivitis, corneal ulcers and other types of eye problems, optometrists in his practice are already trained to do this. "We have an optometric fellowship program where they spend a year learning advanced glaucoma and refractive and corneal management skills," he says. "The optometrists are well-trained in managing very complicated cases of glaucoma, Fuchs' dystrophy, keratoconus, as well as the typical patients with uveitis, conjunctivitis, and pre- and postoperative care. The supply of optometrists seems to be adequate, so I don't see a tremendous demand for PAs to do eye care in our area."

In contrast, he says that PAs would be more helpful to family practitioners or internal medicine doctors, because there is a shortage of them coming into practice in his area of the country. "To be useful in an eye care practice, PAs need to be able to do analysis of the optic nerve, evaluate retinal detachments, check IOP, look for corneal ulcers, remove corneal sutures, etc.," says Dr. Hardten. "They could be trained to do that, but it seems unlikely that this would be incorporated into most PA school training, but I'm sure a special yearlong training program could be created for this should there ever be a heavy demand for these skills. This could be a relatively lengthy training program, however, so they may not want to go through another year of schooling when they could go ahead and go into the workforce in the typi-

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cal fields that a PA might work. In our practice, we don't currently perceive the need for advanced eye-care management by PAs."

Practicing Ophthalmology

Some believe that PAs could play a different role than optometrists and techs. In 2011, Rachel Reinhardt, MD, wrote a white paper about the future of physician assistants in ophthalmology that was presented at the AAO's annual meeting.[1] She conducted a review of all 50 states' statutes and regulations and found that 22 states "have some degree of potential restriction of PA practice that could limit their scope in ophthalmology." Twelve of those 22 states have only a small limitation of scope that generally restricts them from performing refractions or prescribing glasses or contact lenses.

However, the paper supports PAs practicing in ophthalmology practices and says they have a role that is different from that of optometrists: "If PAs enter the field of ophthalmology, it will not be to replace or duplicate the ophthalmologist, optometrist or technician, but rather to carve out a unique role in a future where ophthalmologists will be in demand."

She adds that, "In this age of attempted expansion of optometry scope of care, including attempts and some successes, to expand optometric care to include surgery, PAs offer hope to patients and ophthalmologists. Unlike technicians and optometrists, PAs are licensed to practice medicine with physician supervision. Unlike technicians, PAs can bill for any service the physician can do. Unlike optometrists, PAs have a purely medical and surgical education. The physician-physician assistant relationship is the foundation on which the PA field has been built, and PAs are dedicated to the concept of physician-led care."

She also notes that, "PAs can handle the routine cases in order to free up the ophthalmologist to care for the more complex medical and surgical patients for which their extensive training provides. The physician-physician assistant team would be a benefit to the future of ophthalmology." REVIEW

1. Reinhardt RCJ. A white paper on the future of physician assistants in ophthalmology. Presented at the 2011 annual meeting of the AAO in Orlando. http://www.aao.org/member/related/upload/LDPXIII-2011-Abstracts.pdf.



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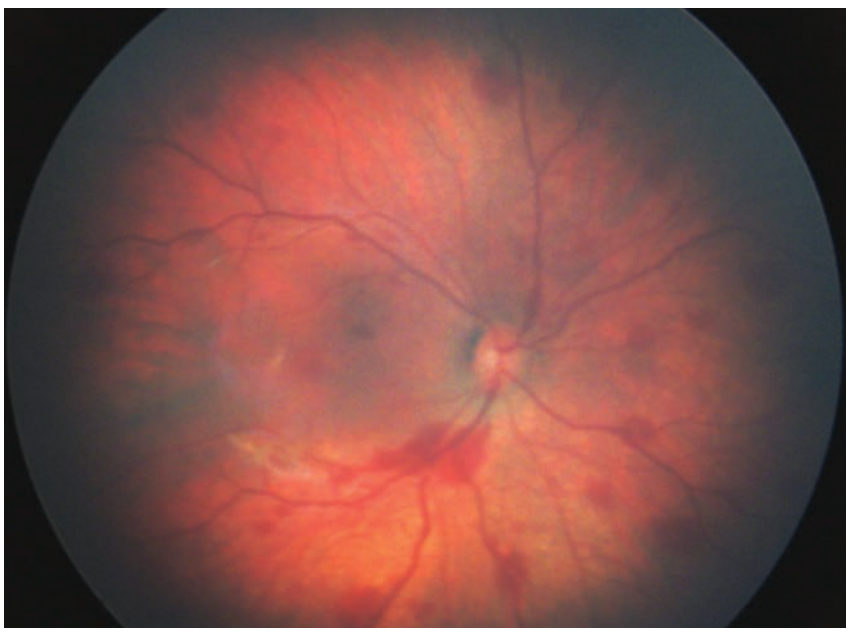
Telemedicine in Pediatric Retinal Disease

Retinopathy of prematurity screening has succeeded where other efforts in telemedicine have not and offers lessons for broader use.

Darius M. Moshfeghi, MD, Stanford, Calif.

Telemedicine can be broadly defined as the remote interpretation of a patient for the purpose of screening, diagnosis and monitoring. In ophthalmology it has been used with variable success in adult populations for screening of diabetes and glaucoma.[1,2] In addition, variations of traditional physician-guided telemedicine have been employed for home monitoring of macular disease that relies on patient-centric monitoring, specifically the ForeseeHome device-based system and the DigiSight smartphone-based system.[3,4] Google and Alcon have recently announced a partnership to commercialize a contact lens-based insulin monitor for patients with diabetes, and a similar system is also being developed for intraocular pressure monitoring in patients with glaucoma.[5,6] These approaches have taken a while to gain market penetrance due to resistance from patients and physicians, based upon both technological and financial hurdles. It has been difficult to develop a financial model that makes sense for both the physician and the patient, creating a barrier to wider acceptance, and patients have demonstrated resistance to spending money for preventive care.



Right eye. Scattered subretinal blot hemorrhages sparing the fovea in a normal-term infant.

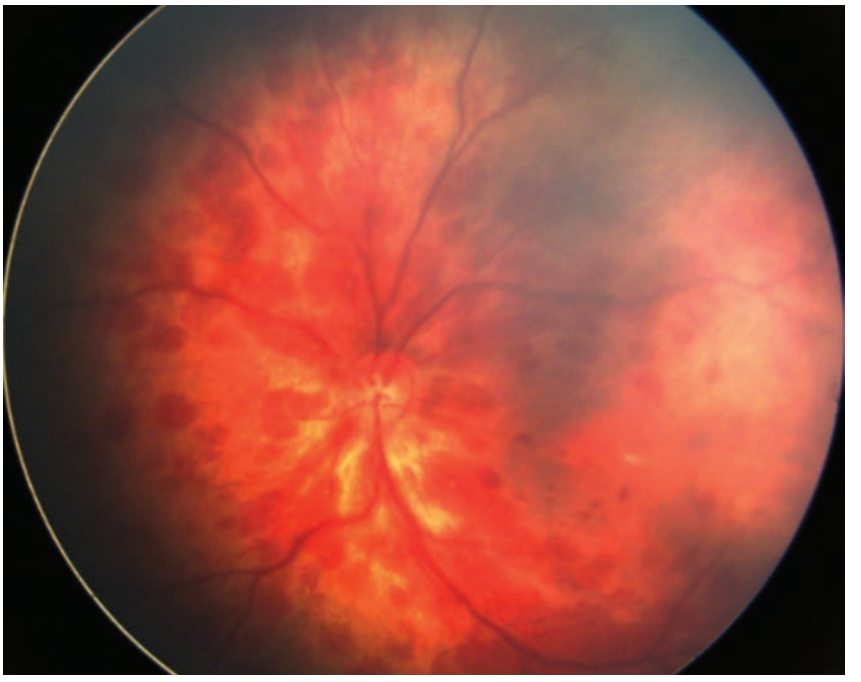
Partly, this is a problem of casting too wide a net—if one screens for all diabetic retinopathy, one is likely to find a lot of diabetic retinopathy that does not need intervention, ironically increasing the burden on the same physicians it is intended to be assisting. A notable exception has been for retinopathy of prematurity screening. This application has worked for three simple reasons: 1) the remote screening is highly effective at identifying a treatment intervention time point; 2) the disease is self-limited in that it will

This article has no commercial sponsorship.

either spontaneously resolve or result in retinal detachment and blindness within a 15-week time frame; and, 3) all neonatal intensive care units (NICUs) are required to perform screening in order to maintain accreditation, removing most of the financial uncertainty. These three components give us great insight into greater application of telemedicine in ophthalmology. First, let us review the ROP scenario.

ROP Telemedicine

ROP screening with wide-angle, fiber optic cameras was demonstrated to be feasible in the early 2000s,[7] equivalent to bedside indirect ophthalmoscopy for detecting any ROP in the PHOTO-ROP trial,[8] able to detect treatment-warranted ROP (e.g., Type 1 disease: Zone I and Plus OR Zone I and Stage 3 OR Zone I or II, Stage 3, with Plus) in the SUNDROP experience,[9] and equivalent to BIO for detecting referral-warranted ROP (similar to Type 1 disease) in the e-ROP trial.[10] Basically, remote digital fundus imaging (RDFI) using wide-angle cameras (130 degrees) captured all treatment inflection points for whatever ROP severity was present. This does not mean it identified all disease; in fact, in the SUNDROP experience, it has been shown that oftentimes disease exists that is detected on BIO, not on camera. However, this disease is in Zone III and would not trigger a treatment intervention using current guidelines. This is an important point: Telemedicine screening is designed to monitor for treatment inflection points, not capture of all disease. Noting the success of these endeavors, the Joint Statement Screening guidelines were updated in 2013 to allow for telemedicine screening of ROP,[11] and the American Academy of Pediatrics recently issued a joint technical report on telemedicine screening for ROP in 2015 which concluded "… evidence of moderate (levels II and III) quality supports the use of RDFI to identify patients with clinically significant or referral-warranted ROP for ophthalmic evaluation and management."[12] The SUNDROP network, which I founded in 2005 at Stanford University, has the longest experience in provision of telemedicine screening services for ROP in the United States. This is a community outreach project, which provides underserved NICUs with access to quaternary ROP experts. Its success has been predicated in no small measure on the fact that it has been financially sustainable from the beginning because of the NICU requirements. We have developed a partnership with our member NICUs to endeavor to prevent follow-up miscues upon discharge of the patients. Review of medical records indicates that most blindness from ROP occurs because of lack of screening for one reason or another, as opposed to actual treatment failures. This has placed a greater onus on expanding the screening to cover all eligible patients. The success has empowered everyone to maintain a culture of pride about prevention of blindness in this at-risk population.



Left eye. Multiple near-confluent white-centered subretinal hemorrhages in the macula, peri-papillary and extramacular locations.

Universal Screening of Newborns

Pediatric vitreoretinal surgery physicians have been looking to expand upon the success of telemedicine screening for ROP. One potential opportunity is universal screening of newborn infants. In China, Brazil, Hungary and Spain, universal screening has been practiced in single-hospital settings for up to seven years. There has been remarkable similarity of findings across diverse populations: 10- to 20-percent incidence of fundus hemorrhages, and 1- to 2-percent incidence of all other pathology.[13] This is of great importance for two reasons: 1) the 2-percent incidence of non-hemorrhage pathology meets the 2-percent incidence threshold for a screening program to have socioeconomic benefit if performed on a large scale in a general population; and, 2) depending on socio-economic

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Thoughts on Cataract Surgery: 2015

How one leading surgeon **is adjusting his approach** to cataract surgery to meet today's new challenges.

By Richard Lindstrom, MD

Cataract surgery is the most common procedure performed by the ophthalmic surgeon. This year, 3.6 million cataract procedures will be performed in the United States and more than 20 million will be performed worldwide, according to estimates. In spite of these impressive statistics, the number of patients visually handicapped by cataract globally increases every year.

In the United States, there are approximately 18,000 ophthalmologists, of whom 9,000 perform cataract surgery regularly. Thus, a typical surgeon might anticipate a surgical volume of about 400 eyes per year. National statistics in other specialties, such as cardiovascular surgery and orthopedics, suggest that a surgeon who performs more than 50 procedures per year generates a significantly lower complication rate; for an institution, the threshold number is 200. America's cataract surgeons and the institutions where they work almost universally reach these numbers, which is encouraging for the potential patient. Still, the cataract operation of today is far from perfect, and because vision is so important to quality of life, everyone engaged in this marvelous sight-restoring procedure is highly motivated to seek continuous improvement in outcomes. Here, I will share some thoughts on what I am doing in 2015 to enhance my patient outcomes.

Preoperative Issues

In the preoperative examination, I do more testing and objective screening, usually at my own expense, since most third-party payers will not pay for these tests. Approximately 25 percent of my patients opt for a so-called premium option, which includes a desired refractive outcome to reduce their dependence on glasses. I call this refractive cataract surgery, and I discuss this option with all patients. In order to properly determine who is a good candidate for refractive cataract surgery, I find screening for hyperosmolarity and dry eye with the TearLab device, irregular astigmatism, astigmatism axis and ectasia with corneal topography, and subtle macular changes with optical coherence tomography all to be indispensable. These tests are therefore a routine part of my current exam.

As a corneal surgeon who also treats a lot of glaucoma, my preop testing may also frequently include pachymetry, goniscopy, specular microscopy, visual fields and OCT of the optic nerve. In summary, I am doing a lot more testing, and in the Accountable Care Act era with the triple aim of excellent outcomes, highly satisfied patients and reduced cost, the extra cost is usually borne by me. The 25 percent of patients who opt for refractive cataract surgery helps cover these costs, as does the fact that my partners at Minnesota Eye Consultants and I perform most of

our surgery in an owned ambulatory surgery center. As I have suggested in several editorials in *Ocular Surgery News*, the triple aims of the accountable care act will in large part be achieved on the backs of the physician provider. Such is the state of modern-day U.S. practice.

Intraoperative

In 2013-2014, I worked to incorporate femtosecond laser-assisted cataract surgery (FLACS) into my practice, but in 2015 it will play a minimal role. I like FLACS and find it fun to do, but simply cannot afford it in my current practice environment. I am passionate about the ocular surface, and also advocate for protecting it during surgery. I therefore treat the corneal epithelium with the same respect most surgeons reserve for the corneal endothelium. I find a dispersive viscoelastic on the ocular surface, especially when warmed in an incubator to 34 to 37 degrees C, to be extremely effective in protecting the ocular surface during surgery. In addition, the surgeon view is enhanced and no irrigating with BSS is required during the procedure, freeing the scrub nurse for other tasks.

Even after 40 years, it is still a pleasure to restore … and enhance a patient's vision.

In those patients with evidence of significant ocular surface disease, I perform what I call ocular surface preparation. Most patients do not want to wait more than two weeks to schedule their surgery. For me, the most rapidly acting agent for ocular surface preparation is a topical corticosteroid. I usually combine it with an antibiotic using one of the combinations drops such as tobramycin/dexamethasone or tobramycin/loteprednol 4X daily, along with artificial tears (usually Systane Balance or Blink), hot packs (Bruder Compresses are convenient and effective), lid hygiene(I Lid Cleanser from NovaBay and, in recalcitrant cases, Cliradex) and 2 grams a day of a quality omega 3 (PRN or Nordic Natural). I want corneal staining absent before surgery whenever possible. I am increasingly aware of and aggressive in the preoperative management of ocular surface disease. I also pretreat with an NSAID for three to seven days, with duration depending in large part on a given patient's risk for postoperative inflammation and cystoid macular edema. If I am using a topical corticosteroid, I prescribe it before surgery for use the same number of days. The NSAID and corticosteroid are synergistic, and no additional cost is generated.

After decades of performing and teaching corneal relaxing incisions, today I manage astigmatism in most patients with an on-axis incision or a toric IOL. I mark the steeper and flatter meridian during surgery using a surgical keratoscope (Mastel). This eliminates issues with globe rotation and, for me, is more than accurate than preoperative marking. I factor the findings of Doug Koch, MD, on posterior corneal astigmatism into my management plan, as, to date, I do not have an instrument to measure posterior astigmatism accurately.

I have found intraoperative aberrometry enhances my refractive outcomes (Verifye, WaveTec). The average patient in America who presents for cataract surgery is 69 years of age with only a mild/moderate density of nucleus. For this reason, I have adopted a supracapsular phacoemulsification approach I call tilt and tumble for most cases. I hydrodissect the nucleus with the Chang cannula until it sits vertical within the capsular bag. In some cases, viscodissection with my dispersive viscoelastic is helpful. This approach also works extremely well in patients with small pupils, intraoperative floppy iris syndrome, or IFIS, and pseudoexfoliation cases, which are very common in my practice. I will also "push" the iris back in IFIS cases with Viscoat. In this approach, the nucleus itself dilates the pupil and irrigation is superior to the iris plane, blowing the floppy iris posterior rather than anterior. The use of the soft-shell approach, as described by Steve Arshinoff, MD, with a dispersive viscoelastic (the same Viscoat I have used to protect the corneal epithelium, viscodissect and position the iris in IFIS) and a bevel-down, 20-ga. phaco needle with a hyper-pulse energy profile generates minimal endothelial cell loss. I have also adopted forced-infusion fluidics with the Stellaris and Centurion, setting the intraocular pressure at 55 to 60 mmHg, generating an extremely stable anterior chamber. When needed, the ocular sealant ReSure has replaced sutures. Perhaps most controversial, after three years of intracameral moxifloxacin, I have adopted the intavitreal transzonular injection of moxifloxacin or moxifloxacin/vancomycin and triamcinolone (TriMoxi, Imprimis) for infection prophylaxis and inflammation management.

Postop

My preferred postoperative regimen requires only a single drop when TriMoxi is injected—ILevro or Prolensa once per day at bedtime. I like

my patients to be on an NSAID for four to six weeks in routine cases and eight to 12 weeks in high-risk cases such as those with diabetes mellitus. I also encourage patients to continue with ocular surface treatment as needed. To me, there is an ocular surface rehabilitation required after surgery followed by long-term ocular surface maintenance. At a minimum, I encourage the same artificial tears prescribed preoperatively 4X daily, along with other adjuncts as needed. For many patients, ocular surface disease is first diagnosed in a preoperative examination and lifelong therapy is appropriate and to be encouraged, including adjuncts such as omega 3 nutritional supplements, Restasis, erythromycin ointment or topical azithromycin and low-dose oral doxyclycline (20 to 40 mg a day), when needed.

In refractive surgery patients, I am aggressive with enhancements, which for me are usually LASIK or PRK. I will rotate a toric intraocular lens in select cases, using the astigmatismfix.com guidelines of my partner David Hardten, MD and former fellow John Berdahl, MD, but I find laser corneal refractive surgery to be more accurate for most patients, as I can fine-tune both the sphere and cylinder. I am very reluctant to exchange multifocal or accommodating IOLs, and stall as long as I can and exhaust all other possibilities—especially ocular surface restoration, posterior capsule clarity and residual refractive error management—before performing IOL exchange. Having implanted these lenses for more than 20 years, I find an in-focus, well-centered multifocal or accommodating IOL in a healthy eye is almost always accepted over time by the patient. Exceptions are patients who likely should have never received a presbyopia-correcting IOL, such as those with prior radial keratotomy, significant higher-order aberrations after LASIK or even frank keratoconus, Fuch's dystrophy, glaucoma with significant damage and macular disease, especially unrecognized epi-retinal membranes and age-related macular degeneration.

Cataract surgery fortunately continues to evolve. This field of surgery is economically viable and critical to the ophthalmic surgeon, patient and society, which supports continuing innovation. Even after 40 years, it is extremely satisfying to restore and, in many cases, enhance the vision of a patient handicapped by cataract. REVIEW

Dr. Lindstrom is the founder and attending surgeon at Minnesota Eye Consultants; he is an Adjunct Professor Emeritus at the University of Minnesota, Department of Ophthalmology and a visiting professor at the University of California, Irvine, Gavin Herbert Eye Institute.

(continued from page 35)

laser makes a big difference in getting the effective lens position right. There are still LASIK surgeons using bladed keratomes to make flaps. That's fine, but it doesn't mean that using a laser to make the flap adds nothing to the procedure.

"Last week I had two pseudoexfoliation patients; one agreed to the laser, the other said no," he says. "Thankfully, nothing bad happened to the patient who elected to do a standard procedure, but it was a much harder procedure for me because she didn't have good zonular support in certain areas. The patient who used the laser had a clear cornea and 20/30 vision at the three-hour visit; the other surgery took longer and the patient had corneal edema and 20/80 vision at the three-hour visit. Using the laser does make a difference."

"I think we're starting to see more data supporting the idea that femtosecond cataract surgery does have advantages over traditional phacoemulsification using ultrasound," agrees Dr. Chu. "I agree that traditional cataract surgery is excellent; but once you start using the femtosecond laser, you do see some advantages, and those are beginning to come out in the studies. Patients get quicker visual recovery because there's less ultrasound energy, and there's less inflammation in the eye. We're seeing better refractive outcomes and reduced enhancement rates with our premium IOL patients. So I do believe that over time we'll see the femtosecond laser become an increasingly important part of cataract surgery."

Dr. Stonecipher says he believes the femtosecond cataract laser technology is a worthwhile investment. "Most people are paying off the cost of the technology much more quickly than they expected," he says. "We paid our laser off in three years, and we probably could have paid it off faster than that. Also, many people believe that it matters what part of the country you practice in and who your patient base is. I don't agree. I think what does matter is what you feel is the best technology in your hands."

"The hurdle that's keeping everyone from using femtosecond surgery is the economics and the regulatory environment," Dr. Chu concludes. "Right now it has to be used in a refractive cataract situation; it's an expensive, premium technology. I think some things need to change before it becomes widely adopted as a good surgical tool that's used for all patients. We'll have to wait and see how it plays out, both in the marketplace and in the regulatory agencies." REVIEW

Dr. Chu is a consultant to Bausch + Lomb. Dr. Stonecipher is a consultant for Alcon, Bausch + Lomb and LenSx, and is a speaker for LENSAR and Abbott Medical Optics. Dr. Singh is a consultant and speaker for Bausch + Lomb.

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Sampling New Targets For Allergy Therapy

Learning more about ocular allergy has revealed a host of potential allergic mediators for researchers to attack.

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

The hunt for new therapeutics is daunting. Beyond the initial matchmaking of drug candidate and cellular target comes a string of hurdles—some sequential and many parallel—that include preclinical testing, formulation, manufacturing, stability, toxicology and clinical confirmation. As our knowledge of the myriad physiological pathways regulating the ocular surface has expanded, the number of potential targets for therapeutic intervention has grown. But the goal is not simply to accumulate prospects, but rather to identify and develop new treatments that address unmet needs.

In ocular allergy, we are well-served by the currently available cadre of antihistamines, anti-inflammatories and mast cell stabilizers, yet there remains a significant need for therapies that can alleviate chronic allergy and ocular inflammation. Most anti-allergic drugs target the mast cell and its chief minion histamine, but these cells are only one step in the ocular allergic cascade, and their activation frees a kaleidoscope of allergic mediators in addition to histamine. Many of these are molecules that we've examined over the years, while others, including those derived from neighboring tissues, have come to our attention only recently. This month we survey findings on new potential targets for therapeutic treatment of ocular allergy.

Mast Cells: An Allergic Nexus

Mast cells have been the target for most allergic therapies because of their role in the response to allergen exposure.[1] In an atopic response, the exposure to antigen involves processing of the offending agent—pollen, dander or dust mite—by antigen-presenting dendritic cells. These cells signal a stepwise activation of T and B lymphocytes, and eventual production of an allergen-specific IgE antibody. These steps are part of the adaptive immune process that's hijacked in the development of allergic conjunctivitis and other allergic conditions.

When mast cells are activated by binding of the complex of allergen, specific IgE and IgE receptors ($F_c\varepsilon Rs$) expressed on the mast cell surface, a cascade of cellular events is initiated that includes the release of pre-formed allergic mediators and the synthesis of additional lipid-derived signaling compounds. At this point it may seem self-evident that since mast cells elicit allergic responses, and mast cells release histamine, histamine must be responsible for the allergic response. But this hadn't been established when we began looking at histamine levels in tears and the association between those levels and ocular allergic disease.[2] While we've established that antihistamines have a high degree of efficacy in relieving signs and symptoms of AC, there are still many patients who are not well-served by these compounds.[3]

In addition to histamine, mast cells package and secrete proteoglycans, various hydrolases and signaling molecules, including interleukins, tumor necrosis factor and platelet activating factor.[1] Lipid metabolism triggered by phospholipase A2 activation generates prostaglandins, leukotrienes and other lipid-based signaling molecules. In theory, all of these compounds represent potential targets for allergy therapy, and many have been investigated.

Mast Cell Targets

In previous installments of Thera-

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peutic Topics, such as the May 2013 column, we discussed the importance of a number of protein kinases as potential targets for allergic therapy. Allergen cross-linking of the $F_c\varepsilon RIs$ leads to activation of a series of kinases that provides the link between allergen and mast cell degranulation and activation.[4] For example, one of the earliest responses to surface antigen-antibody binding is phosphorylation of Lyn kinase, an enzyme that responds to this phosphorylation by physically associating with the antibody-receptor complex on the intracellular side of the cell membrane, initiating subsequent phosphorylation events. Spleen tyrosine kinase (Syk), phosphoinositide 3-kinase, and protein kinase C all participate in the activation chain, and so all are potential targets for intervention. Based upon issues of pharmacokinetics and tissue specificity, it turns out that Syk appears to be the best of these potential choices. There are small molecule inhibitors of Syk in development for a number of disorders, and their future testing in models of ocular allergy may not be far off.[5] Interestingly, a Japanese laboratory studying therapeutic effects of plant glycosides has identified Syk kinase inhibition as a potential mechanism in the treatment efficacy of *Camellia japonica* extracts in models of both allergic rhinitis and conjunctivitis.[6]

Lipid-derived signaling molecules include prostaglandins, leukotrienes and PAF. Compounds that block cyclooxygenase, such as ketorolac or other NSAIDs, have been used in chronic allergy as steroid-sparing compounds, and they have demonstrated some efficacy, especially in VKC.[7] Several recent clinical studies showed that another NSAID, pranoprofen, compared favorably with a topical steroid in patients with AC.[8] In contrast to these results, our pilot studies testing the responses to topical leukotrienes showed little or no allergic responses. More recent trials of leukotriene inhibitors such as montelukast have confirmed that leukotrienes have little or no role in the etiology of AC.[9]

Studies suggest that the leaves of various species of *Camellia* are a rich source of compounds with potential as therapeutics for ocular allergy.

Studies dating back a decade or more demonstrated that PAF is chemotactic for eosinophils, and that this PAF-mediated chemotaxis has been shown to contribute to the chronic phase of allergic rhinitis and conjunctivitis.[10,11] In addition, PAF induces degranulation of eosinophils and increases vascular permeability, two effects associated with chronic-phase allergy. The permeability response is separate from that elicited by histamine, as it isn't blocked by antihistamines such as olopatadine.[12] Despite this, most research efforts on PAF have focused on its role in neuropathic and cancer-related pain.[13] With renewed interest in finding therapies for more chronic allergic conditions, it may be time to give PAF a second look.

Tackling Allergic Inflammation

A significant part of perennial and chronic allergy is ocular inflammation and the associated infiltration of inflammatory cell types into the ocular surface environment. Established mast cell pre-formed mediators such as TNF-α are thought to be involved in this process as either direct chemoattractants or as instigators of inflammatory cell recruitment. Recent studies of TNF-α in pre-clinical models of ocular inflammation suggest that topical use of inhibitors can reduce both inflammatory cell recruitment and production of inflammatory cytokines such as IL-6.[14] Perhaps the one-two punch of an antihistamine, which blocks the acute effects of degranulation, and an anti-allergic, which blocks TNF-α-mediated inflammation, could provide a more comprehensive anti-allergic response than the presently available therapeutic compounds, whose efficacy against severe ocular allergies is lacking.

Yet another approach to inflammation involves intervention beyond the mast cell. A key cytokine in inflammatory signaling is thymic stromal lymphopoietin, an epithelial cell-derived molecule that acts to shift adaptive responses toward a sensitized, allergic phenotype.[15] In the eye, TSLP appears to enhance allergic responses of antigen-presenting dendritic cells and mast cells, and it appears to have a role in the underlying etiology of AKC.[16] In a recent clinical trial, treatment of asthmatic patients with a monoclonal antibody to TSLP reduced allergen-induced bronchoconstriction and indices of airway inflammation both before and after allergen challenge.[17]

Monoclonals as Topicals?

Among current therapies, mast cell stabilizers such as pemirolast act at one of the earliest points in the allergic cascade, disrupting the linkage between $F_c\varepsilon RI$ activation and mast cell degranulation.[18] While this is an attractive strategy, these drugs are limited by lower efficacy and a require-

ment for pretreatment, both of which reduce their overall utility. An alternative that would also halt the activation process before it starts would be an inhibitor like omalizumab, a humanized monoclonal antibody that binds to the CH3 domain near the binding site for the high-affinity type-I IgE F_c receptors of human IgE. Omalizumab can neutralize free IgE and inhibit the IgE allergic pathway without sensitizing mast cells or other cell types with surface $F_c\varepsilon RI$ receptors such as those found on basophils.[19] Although this mechanism requires the mAb to be used in an injectable form, a recent report demonstrated its efficacy as a treatment for a case of severe VKC.[20] Another potential target for mAb therapy, particularly in severe conditions such as AKC or VKC, is the IL-4 mAb Dupilumab (Regeneron), currently in development for atopic dermatitis.[21]

As in other disorders, use of mAbs targeting other candidates for allergic intervention—interleukins or interleukin receptors, for example—will sink or swim based upon issues of pharmacokinetics. Even monovalent antibody fragments are extremely large molecules by pharmaceutical standards, and wouldn't be expected to appreciably penetrate ocular tissues when applied topically. Despite this, a number of published studies have provided encouraging evidence that topically applied mAbs can have a therapeutic impact on the ocular surface. In several recent trials employing the topical VEGF inhibitors ranibizumab or bevacizumab as a treatment for corneal neovascularization, both treatments were able to reduce vascular proliferation.[22,23] This finding establishes a proof of principle that even molecules as large as mAbs can be of benefit when delivered topically. While their therapeutic utility may be limited to the most severe cases of allergy with epithelial damage, they also can help to establish suitable targets for small molecule discovery.

Like the Japanese *Camellia* leaves that are used to make tea (and potentially, Syk inhibitors), another potential anti-allergic comes from an unlikely place: the kitchen. It turns out that turmeric roots, members of the ginger family that are commonly used as spices (especially in Indian foods) are also the source for curcumin, a polyphenol compound with multiple therapeutic applications. Among these is an ability to suppress responses to allergen challenge in a mouse model of allergic conjunctivitis.[24] Our own mouse model has been designed to test compounds that target both the acute, early phase (antihistamine) response, as well as later stage chronic (anti-inflammatory, steroid-like) responses. We know from our own studies that this pre-clinical confirmation of efficacy is an important step in the overall process of discovery. *(McLaughlin JT, et al. IOVS 2013; 54: ARVO E-abstract 2553)* In fact, the endpoints evaluated in early animal efficacy work mirror those that will ultimately be evaluated in the clinic, thus increasing the translatability of preclinical efficacy into success in the final stages of development.

It seems that we don't have to look too far to find many potential targets for new therapies to treat ocular allergies, but as always, the real effort comes in sorting the true contenders from the false pretenders. Still, it's encouraging to see that many of the newest treatment candidates have shown the promise of addressing our biggest current unmet need: chronic allergic conjunctivitis. REVIEW

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Are Two MIGS Surgeries Better Than One?

Using multiple stents or combining options that affect different pathways may increase their pressure-lowering capacity.

L. Jay Katz, MD, Philadelphia

One of the frontiers in glaucoma treatment today is a group of surgeries referred to as minimally invasive glaucoma surgeries, or MIGS. The primary advantage of these procedures, which currently include the iStent, the Trabectome and endoscopic cylcophotocoagulation, is that they involve far less risk for the patient than options such as trabeculectomy and tube shunts. Furthermore, because they are *ab interno* procedures, they can be performed through a cataract incision, making them ideal for combining with cataract surgery. The perceived drawback to these procedures is that they tend to produce a smaller pressure reduction than the other surgeries mentioned. As a result, they're often thought of as intermediate procedures—kind of a bridge to more invasive surgeries that may lower IOP more dramatically.

Today, however, as surgeons become more familiar with these options and more of them make it through the Food and Drug Administration approval process, a new possibility is arising: Increase the pressure-lowering power of these procedures by multiplying them. That can be done in two ways: in the case of a given device, by implanting more than one; and in general, by combining different MIGS approaches—in particular those affecting different mechanisms and pathways.

Using Multiple Pathways

The options we have for maximizing the effectiveness of MIGS procedures in many ways parallel what we can do with pharmaceuticals. For example, we can aim to lower IOP by maximizing a single outflow pathway using multiple drugs that affect that pathway, or by using two aqueous suppressants such as beta-blockers and carbonic anhydrase inhibitors. I think this is much like placing multiple iStents in the trabecular meshwork, which the data suggests lowers pressure more than a single stent.

On the other hand, a lot of what we do with drugs involves lowering pressure by enhancing multiple pathways. We can lower pressure by decreasing aqueous production, but we also have drugs that enhance uveoscleral outflow, such as prostaglandins, and some newer drugs under investigation like rho kinase inhibitors and adenosine agonists that enhance trabecular outflow. (Another new drug, latanoprostene bunod, has a complex molecule that affects both trabecular outflow and uveoscleral outflow.) Experience has confirmed that combining drugs that act on different pathways can increase the amount of pressure reduction, so acting via multiple mechanisms is a reasonable approach.

The idea of combining treatments is now beginning to show up in the MIGS arena. The early data that's being reported indicates that combining pathways through multiple MIGS procedures can increase the amount of pressure reduction we can achieve. For now, this data is limited, partly because many potential MIGS devices are still awaiting approval by the FDA. For example, the devices intended to enhance uveoscleral outflow, including Transcend Medical's CyPass and Glaukos's iStent Supra, are not currently FDA-approved, and the Xen Gel Stent (from AqueSys), an *ab interno* device designed to allow outflow to the subconjunctival

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space, is also still in the pipeline. However, some surgeons are actively combining the currently approved MIGS procedures with good results. In particular, performing ECP and implanting an iStent during cataract surgery—sometimes referred to as the ICE procedure—has surgeons reporting positive outcomes. *(See Putting Glaucoma on ICE, right.)* And Glaukos, manufacturer of the iStent, is looking into the possibility of maximizing pressure reduction by combining the trabecular and uveoscleral pathways. This makes sense because they have stents that address each of those pathways; the current iStent and the (not approved) iStent Inject are designed to enhance trabecular outflow, while the (not approved) iStent Supra is intended to enhance uveoscleral outflow.

Which Combination to Use?

One question this raises is whether one particular combination of procedures (and/or outflow pathways) would be more effective at reducing IOP than another. Of course, we have no clinical trial data on which to base such a comparison right now, but even if clinical trials eventually compare different combinations of MIGS procedures, the results might not tell us which combination would work best in a specific patient. This is certainly true for drugs; if a trial compared a fixed combination of a beta blocker and prostaglandin to a beta blocker-brimonidine combination, you might get a bigger average drop in one group than the other, but an individual patient might not mirror that finding. So a trial wouldn't necessarily tell you which choice is best for the patient seated in front of you.

The nature of the glaucoma, the age of the patient, the stage of the disease, how elevated the pressure is—all of these factors, and possibly others, may determine which combination of procedures will work best for a given individual. You might choose a different combination of MIGS procedures for a patient who has a relatively low IOP but is progressing than for someone with high-tension glaucoma, just because it makes more sense based on the pathophysiology of the disease. With glaucoma drugs (for now, at least) it's trial and error because of the difficulty of predicting the efficacy of a given treatment. And that will probably also be true when combining MIGS procedures.

Of course, another factor that will affect which combination a given surgeon might end up using is the surgeon's own preference and comfort level, as well as which techniques he or she happens to learn. If all the options were approved, some surgeons might feel most comfortable combining a Xen Gel implant and a Hydrus. Others might prefer combining ECP and Trabectome, or prefer combining the iStent Inject and the Supra. So which procedures a surgeon ends up using will be partly determined by the patient's condition and partly by the surgeon's knowledge and comfort level.

Putting Glaucoma on ICE

The combination of simultaneous inflow and outflow procedures makes sense for many reasons. One need only look at how we treat glaucoma with eye drops (using both agents that reduce aqueous production and those that enhance its outflow) to see that combined inflow and outflow strategies can be complementary and synergetic. (There is no existing evidence to suggest that one strategy is better than the other for the preservation of visual function.) The potential disadvantage of combining several strategies for traditional glaucoma surgery would be a concern that hypotony might become more of an issue. Fortunately, in the microincisional glaucoma surgery space, hypotony is not a significant concern because we are not typically performing full-thickness filtration procedures.

Shortly after adopting trabecular micro bypass using the iStent (from Glaukos), some colleagues and I began combining cataract extraction, endocyclophotocoagulation and trabecular micro bypass to form the ICE procedure (iStent-cataract-ECP). Mechanistically, the procedure should provide increased trabecular outflow, decreased aqueous production and a likely increase in both trabecular outflow from angle widening and possibly some reduced aqueous production as a result of the cataract surgery.[1-3]

In a series of 70 moderate glaucoma patients who underwent the procedure, we noted that the procedure was as safe as standard cataract surgery.*(Radcliffe N, Noecker R, Sarkisian S, Parikh P. ICE Surgical Technique Outcomes: MIGS Implantation of Trabecular Bypass Stent, Cataract Extraction, and Endoscopic Cyclophotocoagulation. 2014 American Glaucoma Society Annual Meeting, Feb 27-March 2, 2104, Washington, DC.)* ECP can create some additional inflammation, but this does not affect the visual outcome if managed appropriately. From a baseline intraocular pressure of 19.4 mmHg, the pressure was reduced to 15.8 mmHg by the three- to six-month visit. While about 60 percent of patients used two or more medications prior to the procedure, only a quarter remained on this many medications after. Note that the procedure did not work for everyone—at least 20 percent of patients experienced minimal or no pressure reduction.

Currently, I offer this procedure to patients with moderate glaucoma damage who are on at least one medication; sometimes I offer it to "tough-to-treat" patients with early glaucoma who are on several medications. I avoid using the procedure on patients with advanced glaucoma, who would likely require more aggressive and riskier interventions.

In summary, the ICE procedure is important not simply because of the combination of these specific procedures, but because it illustrates the potential of combining future inflow and outflow MIGS procedures, as well as combining future dual outflow procedures that take advantage of different outflow pathways.

— Nathan Radcliffe, MD

More of a Burden?

What about the burden that performing multiple procedures places on the surgeon and the eye? This really is the infancy of our use of MIGS procedures, but in comparison to other traditional procedures for lowering intraocular pressure these procedures are generally easier on both the surgeon and the eye—even if we do two of them. Most of these procedures can be done through the same single incision; there's no need to make a second incision (except in some ECP cases). You go in with one instrument and place one type of stent; you come back out and go back in through the same incision and put a different stent in a different part of the anatomy. In the case of ECP, you use the same incision (and possibly a second one) to put the probe into the eye and apply the laser. I believe this compares quite favorably to trabeculectomy and tube shunt procedures in terms of complexity, time spent and trauma to the eye.

The other reality is that the amount of foreign material being implanted in the eye in MIGS procedures is miniscule compared to something like a tube shunt (or for that matter an intraocular lens), even if you implant multiple stents. Of course, they are utilized for different purposes and they're placed in different parts of the eye, but the comparison is worth noting. (The downside of the small amount of material implanted in MIGS procedures is that the success of most of them requires a great deal of finesse in terms of understanding the anatomy of the eye and the proper placement of these devices.)

Building the Foundation

For now, we're refining the use of the existing devices to maximize their individual effectiveness. For example, the work done with the iStent by Ike Ahmed, MD, suggests that the success of iStent surgery may be linked to determining the location of the most functional collector channels before placing the iStent.

We're also learning about conditions that contraindicate specific MIGS approaches. For example, patients who have Sturge-Weber syndrome with a facial hemangioma typically have elevated episcleral venous pressure, countering aqueous outflow. If the episcleral venous pressure is 30 mmHg instead of the normal 10 mmHg, you're not going to get a pressure reduction by clearing out the resistance in the trabecular meshwork with a stent or Trabectome. Instead, the surgeon might want to favor other pathways, such as using a Xen Gel Stent to generate subconjunctival filtration or reducing aqueous production with ECP.

In the meantime, trabeculectomy and tube shunts remain valuable surgical options. But I believe MIGS procedures will increasingly be considered in certain patients—whether it's a single MIGS approach, or a combination approach—to eliminate the need for resorting to a trabeculectomy, or at least delay that need. The reality is that when managing glaucoma, we're always trying to postpone progression with medications, lasers or surgery; we never cure the disease. So the more time and options we can offer to patients with safer procedures, the better.

A Great Opportunity

Of course, we're just beginning to figure out which MIGS approaches will make the most sense for each patient. Not all of the devices out there will be approved, but hopefully many of them will be, and new modifications and options will be developed. If we have an arsenal of choices, a lot of surgeons will be applying them, perhaps in various combinations. Future development will be guided by people who are very clever who understand the basic science and the pathophysiology of the various diseases that we refer to as glaucoma.

And that's a reason to be hopeful about the future. The glaucoma microsurgical arena is quite inspiring, and there are a lot of creative people still in their training or in their early years of practice who will make great contributions. We haven't seen a situation like this in a while, where there are so many different possibilities and avenues an individual can take to make a great idea even better. It's a wonderful growth opportunity for bright young people to radically change how we approach surgery for this disease, improving techniques and devices and setting more specific guidelines that better individualize care for patients, getting better outcomes and finding ways to minimize the risks. I firmly believe that over the next decade there will be really important contributions from bright young physicians, scientists who are excited about entering this field. REVIEW

Dr. Katz is the director of the Glaucoma Service at Wills Eye Hospital in Philadelphia. He is a medical monitor and investigator for Glaukos and a medical investigator for InnFocus. Dr. Radcliffe is director of the Glaucoma Service and clinical assistant professor at New York University. He is a consultant for Glaukos, Transcend, Alcon and Allergan.

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Ophthalmologist and noted refractive and cataract surgeon.
Minnesota Eye Consultants

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ISRS Members Share Practice Trends

Bilateral intraocular procedures, femtosecond cataract surgery and LASIK volumes are highlights of the latest ISRS survey.

Walter Bethke, Managing Editor

The most recent survey of the U.S. members of the International Society of Refractive Surgery has revealed some interesting trends, including the use of femtosecond lasers for refractive cataract surgery, the propensity of some surgeons to perform intraocular procedures bilaterally and even signs of life in the LASIK market. Here's a look at the survey's highlights with commentary from one of its co-authors, Mobile, Ala., surgeon Richard Duffey. Four hundred eighty-six of 1,022 members opened the survey and it had a response rate of 15 percent. Here's a look at what the ISRS members had to say.

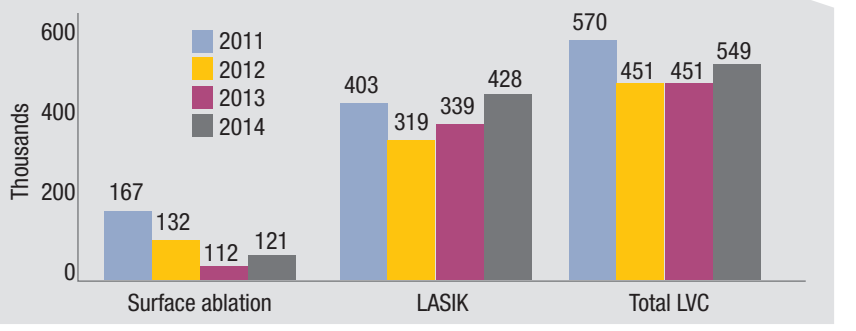
Volume Uptick

Last year marked the first time in several years that there was an increase in the average LASIK volume reported on the survey. The total number of procedures reported was 549,000, which is an increase of 22 percent over last year's 451,000. Dr. Duffey notes though, that many sources still find volumes to be flat, so he'd like to see more data to declare this a solid trend.

"The sample size isn't huge, but it's pretty consistent year in and year out," says Dr. Duffey. "Usually when it shows something, that trend will show on other indicators, as well. But as a general rule of thumb, I like to see a two-year trend. I think this coming year will really tell us if we're truly up or not. I know in my practice I'm up a little from previous years. I hope that we've possibly reached the valley, if you will, and will start to see an upward trend. Some of the trend may be related to the economy, and some may be related to the good press we're getting from the studies sponsored by ASCRS and AAO, as well as the independent studies such as Frank Price's contact lenses vs. LASIK study and PROWL-1 and PROWL-2. So, with a combination of these things, the future is looking a bit better."

In terms of the procedures chosen for particular patients, 40 percent of surgeons say they do some sort of laser vision correction even for high myopes (-10 D). The other popular option for those patients is phakic intraocular lenses (43 percent). For the low hyperope (+3 D), 63 percent of respondents prefer LVC, and 18 percent choose a phakic lens. Fifteen percent say they'd wait. For the high hyperope (+5 D) it tips in the lens's favor, however, with 61 percent preferring to implant a phakic IOL, 9 percent choosing LVC and 19 percent electing to wait.

Volume of Surface Ablation/LASIK Procedures



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Bilateral Surgery

Interestingly, 23 percent of the surgeons say they do bilateral phakic lens implantation. Also, though 67 percent of the respondents usually implant phakic lenses in an ambulatory surgery center and 4 percent operate at a hospital, a fifth of them implant phakic lenses in an in-office modified operating room and 9 percent use a LASIK clean room. Dr. Duffey prefers to use his ASC, but explains where the in-office modified OR and LASIK room fit in: "The move to doing intraocular procedures in these locations is done mostly to save money; when a phakic lens is done, if you take the patient over to the ASC, a lot of your fee goes to the surgery center. I think for some to make it financially viable, they'll establish an environment in their office that's not really a sterile OR and make it as clean as they can.

"I used to have a LASIK clean room," he continues. "It was an extra exam lane that we reserved for lasers. We added an air filter and dehumidifier, and were more conscientious about keeping it cleaner than just a standard exam room. I also use a minor OR in my office in which I do minor extraocular procedures such as pterygium removals, SFKs and conjunctival cyst excisions. I'll rarely repair an emergency corneal perforation in it for a patient who doesn't have insurance, or a gluing procedure for a corneal perforation. It's my own bias, but I wouldn't want to do an elective intraocular procedure in a minor OR where I normally do my external disease surgeries."

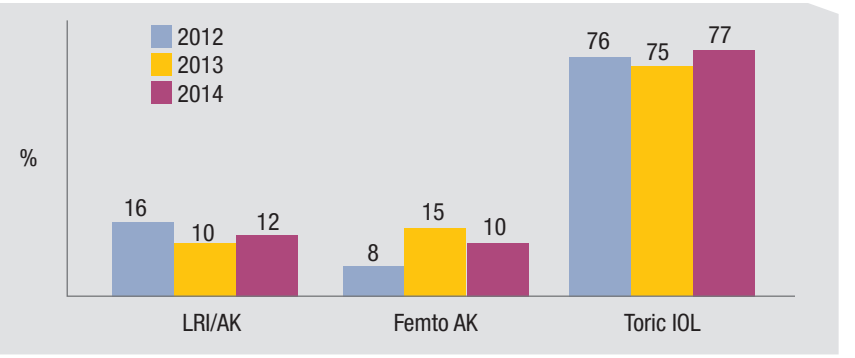
Femtosecond Cataract Surgery

The survey has begun to feel out surgeons regarding femtosecond laser for cataract and correcting astigmatism in conjunction with cataract surgery.

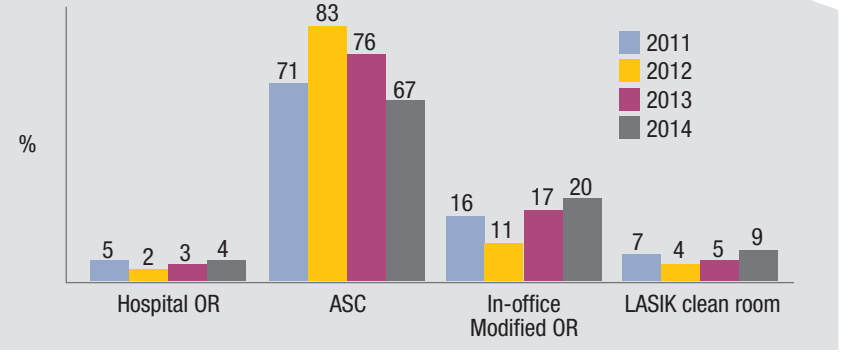
On the survey, the respondents say about 19 percent of their cases are done with the femtosecond laser. What was interesting, however, is that only 54 percent of the respondents use it to correct astigmatism, which was the main reason put forth for using the laser in order to get reimbursed in the first place. Eighty-four percent use it for the capsulotomy and 82 percent to fragment the nucleus. "It's also interesting that only about half use it for the primary and secondary incisions," says Dr. Duffey. "For me, 100 percent include AK. That was the indication that was put out there for it first, yet there are plenty of surgeons on the current survey using it for the capsulotomy and lens fragmentation alone."

Dr. Duffey posits a reason why more corneal entry incisions aren't being made with the femtosecond laser. "In my personal experience, the primary and secondary laser incisions are a little more difficult to open, and placing them exactly at the limbus vs. a little more anterior or posterior can be challenging to accomplish consistently. Sometimes, you get in there and you might wish that you'd been 0.5 mm more anterior or posterior with the incision; you can work around that, however. My biggest issue is that you can't make a primary or secondary incision within 5 degrees of an AK incision. If you try to program it otherwise, the system won't allow it. To eliminate that problem, I just do the capsulorhexis, lens fragmentation and AK with the laser. Then, in the OR, I'll place my primary and/or secondary incisions manually where I want them. If they coincide with the AK, I still go at the same axis, only underneath it. I've spoken with Alcon about it and they say a fix for it will possibly be in a future software update." REVIEW

Preferred Treatment for 1.12 to 2 D of Astigmatism



Location of Phakic IOL Surgery



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Cataract Surgery Safe For Outpatient Clinic

Researchers from St. Elizabeth's Hospital in the Netherlands utilized a retrospective, observational cohort study to determine that cataract surgery can be safely performed in an outpatient clinic in the absence of the anesthesia service and with limited workup and monitoring. Basic first aid and life support skills seem to be sufficient in the case of an adverse event, and a medical emergency team provides a generous failsafe for what is a low-risk procedure.

All patients who underwent elective phacoemulsification/intraocular lens surgery under topical anesthesia in the ophthalmology outpatient unit between January 1, 2011 and December 31, 2012 were included as study participants. Within the cataract pathway, 6,961 eyes of 4,347 patients were eligible for analysis. The primary outcome measure was the incidence of adverse events requiring medical emergency team interventions through the pathway. Secondary outcome measures were surgical ocular complication rates, use of oral sedatives and reported reasons to perform the surgery in the classical operation room complex.

Cataract surgery was performed by phacoemulsification under topical anesthesia. The intake process mainly embraced ophthalmic evaluation, obtaining a medical history and proposing the procedure. A staff ophthalmologist performed the procedure assisted by two registered nurses in an independent outpatient clinic operating room within the hospital. The clinical pathway was without dedicated presence of or access to anesthesia service. Perioperative monitoring was limited to blood pressure and plethysmography preoperatively and intraoperatively. Patients were offered supportive care and instructed to avoid fasting and continue all their chronic medication.

Three medical emergency team interventions related to the phacoemulsification/intraocular lens pathway occurred in the study period, resulting in an intervention rate of 0.04 percent. None of the interventions was intraoperative. All three patients were diagnosed as vasovagal collapse and recuperated uneventfully. No hospital admittance was required. Eight other incidents occurred within the general ophthalmology outpatient unit population during the study period.

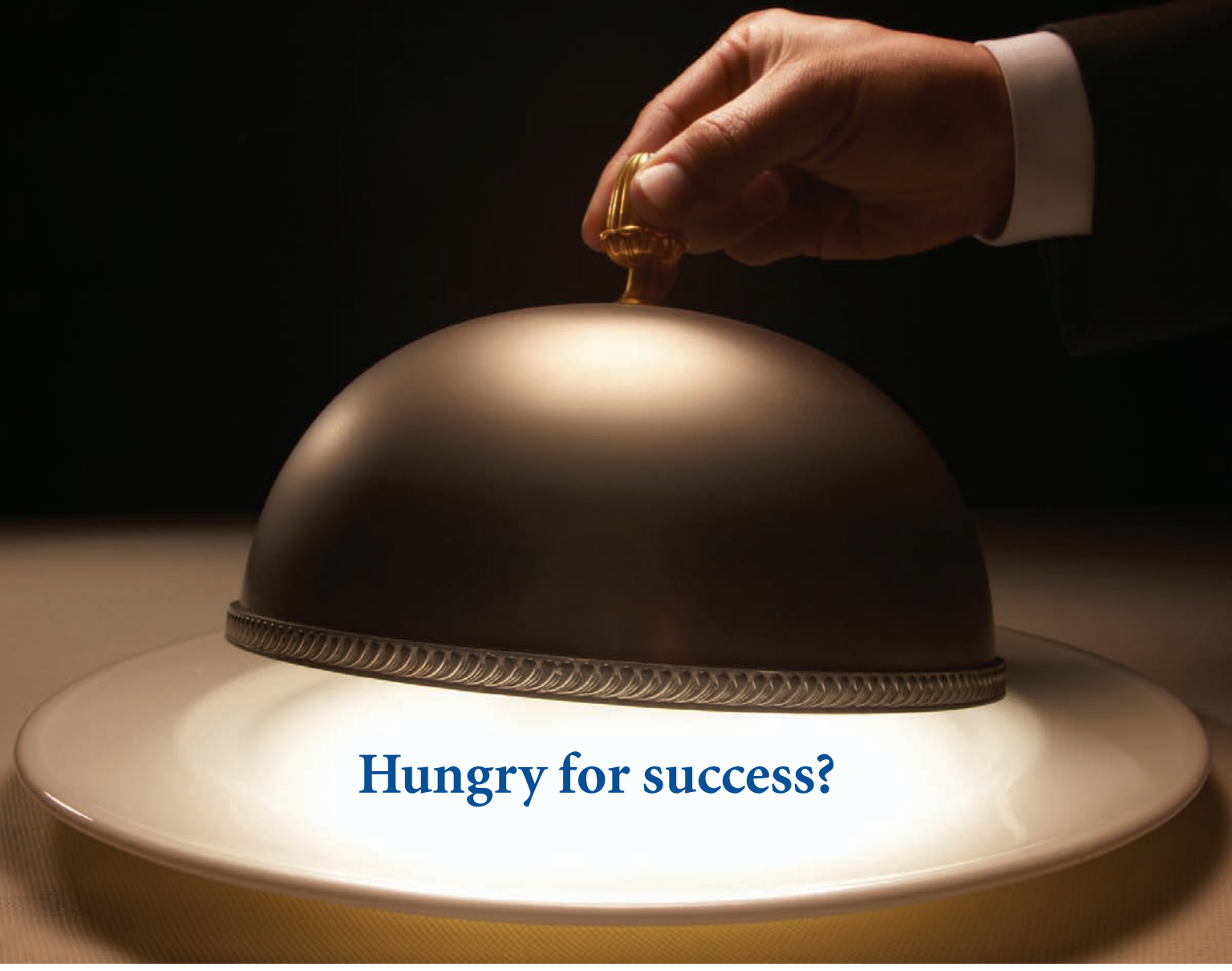
Ophthalmology 2015;122:281-297.
Koolwijk J, Fick M, Selles C, Turgut G, Noordergraaf J, et al.

Central Corneal Thickness Impact on Risk of Glaucoma

New research supports the recent assertion that thin central corneal thickness is a predictor of glaucoma progression and explains a substantial portion of the increased risk of glaucoma seen among blacks and Hispanics.

Patients who were aged 40 years and older in the Kaiser Permanente Northern California health plan from January 1, 2007 through December 31, 2011 with a documented CCT (n=81,082) were included in this cross-sectional study. Patients with any cornea-related diagnoses or a history of corneal refractive surgery were excluded. Demographic characteristics, including age, sex and race/ethnicity, as well as clinical information including glaucoma-related diagnosis, diabetic status, CCT and intraocular pressure were gathered from the electronic medical records.

Multivariate linear regression analysis indicated that female sex, increased age and black race were significantly associated with thinner corneas. A subgroup analysis among Asians revealed that Chinese, Japanese and Koreans had corneas 6 to 13 µm thicker than South and Southeast Asians, Filipinos and Pacific Islanders for each diagnosis ($p<0.001$). Within the patient population, 24.5 percent (n=19,878) had some form of open-angle glaucoma; 21.9 percent (n=17,779) did not have any glaucoma-related diagnosis. Variation in CCT accounted for only 6.68 percent (95 percent confidence interval, 6.14 percent to 7.24 percent) of the increased risk of open-angle glaucoma seen with increasing age, but explained as much as 29.4 percent (95 percent CI,



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27 to 32.6 percent) of the increased risk of glaucoma seen among blacks and 29.5 percent (95 percent CI, 23.5 to 37 percent) of the increased risk of glaucoma seen among Hispanics.

J Glaucoma 2014;23:606-612.
Wang S, Mellex R, Lin S.

DME, Ranibizumab and Prompt vs. Deferred Laser Treatment

Five-year randomized trial results suggest focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better than deferring laser treatment for ≥24 weeks in eyes with diabetic macular edema involving the central macula with vision impairment. Although more than half of eyes in which laser treatment is deferred may avoid laser for at least five years, such eyes may require more injections to achieve these results when following this protocol. Most eyes treated with ranibizumab and either prompt or deferred laser maintain vision gains obtained by the first year through five years with little additional treatment after three years.

Participants were from a previously reported three-year trial evaluating 0.5 mg intravitreal ranibizumab every four weeks until no longer improving (with resumption if worsening) with prompt vs. deferred (for ≥24 weeks) focal/grid laser treatment; of those who consented to and completed the two-year extension, 124 patients (97 percent) were from the prompt group and 111 (92 percent) were from the deferred group. The main outcome measure at the five-year visit was best-corrected visual acuity.

The mean change in visual acuity letter score from baseline to the five-year visit was +7.2 letters in the prompt laser group compared with +9.8 letters in the deferred laser group (mean difference, -2.6 letters; 95 percent CI, -5.5 to +0.4 letters; p=0.09). At the five-year visit, there was a vision loss of ≥10 letters in 9 percent vs. 8 percent of the prompt vs. deferred laser groups; an improvement of ≥10 letters in 46 percent of the prompt laser group vs. 58 percent of the deferred laser group; and an improvement of ≥15 letters in 27 percent vs. 38 percent of the prompt vs. deferred laser groups. From baseline to five years, 56 percent of the participants in the deferred group did not receive laser treatment. The median number of injections was 13 vs. 17 in the prompt and deferred groups, including 54 percent and 45 percent receiving no injections during year four and 62 percent and 52 percent receiving no injections during year five, respectively.

Ophthalmology 2015;122:375-381.
Elman M, Ayala A, Bressler N, Browning D, Flaxel C, et al.

IV Pentamidine Before TKP to Treat *Acanthamoeba* Keratitis

Research from the University of Iowa Hospitals and Clinics on patients treated with intravenous pentamidine before therapeutic keratoplasty for *Acanthamoeba* keratitis suggests that the adjunctive use of IVP before surgery may assist with the achievement of microbiological cure, clear graft and good visual outcome in a majority of cases.

A retrospective medical chart review of every patient treated with IVP before therapeutic keratoplasty for *Acanthamoeba* keratitis at the UIHC between January 1, 2002 and December 31, 2012 found eight eyes of seven patients that met inclusion criteria for the study. Preoperatively, all eight eyes had failed traditional antiamoebic therapy, including five eyes with recurrent infections after previous therapeutic keratoplasty. The patients were treated with IVP (190 to 400 mg/day) for a median of 14 days (r: seven to 26 days). After eight therapeutic keratoplasties, a microbiological cure was achieved and a clear graft maintained in five eyes (62.5 percent) during a mean follow-up interval of 31.2 months (r: one to 95.7 months). Repeat therapeutic keratoplasty in three eyes with recurrent *Acanthamoeba* keratitis resulted in two additional microbiological cures and one more clear graft. The final best-corrected visual acuity was ≥20/40 in five eyes (62.5 percent) and worse than 20/200 in three eyes. Overall, the final vision was improved in six eyes (75 percent), remained the same in one eye (12.5 percent) and was worse in one eye (12.5 percent).

Cornea 2015;34:49-53.
Sacher B, Wagoner M, Goins K, Sutphin J, Greiner M, et al.

Three-year Outcomes for AMD Treat-and-Extend Regimens

Researchers from the Wills Eye Hospital have determined that a treat-and-extend regimen is effective in achieving and maintaining visual and anatomic improvements with neovascular age-related macular degeneration for up to three years of treatment.

The Wills Eye Retina Service treated 212 eyes from 196 patients diagnosed with treatment-naïve neovascular AMD between January 2009 and March 2013; they were treated with either ranibizumab or bevacizumab for a minimum of one year, using a treat-and-extend regimen. The main outcome measures were change from baseline best-corrected Snellen visual acuity, proportion of eyes losing <3 BCVA lines, proportion of eyes gaining ≥3 BCVA lines, change from baseline central retinal thickness and mean number of injections at one, two and three years of follow-up.

The mean follow-up period was 1.88 years (median, two years). At baseline, BCVA was 20/139; it improved to 20/79 (p<0.0001) after one year of treatment and was maintained at 20/69 and 20/64 at two and three years follow-up (p<0.001). At baseline, mean central retinal thickness was 351 µm and significantly decreased to 285 µm, 275 µm and 276 µm at one, two and three years of follow-up (p<0.001). Patients

received, on average, 7.6, 5.7 and 5.8 injections over years one, two and three of treatment. At final follow-up, 94 percent of eyes had lost <3 lines BCVA and 34.4 percent of eyes had gained ≥3 lines of BCVA.

Am J Ophthalmol 2015;159:3-8.
Rayess N, Houston S, Gupta O, Ho A, Regillo C.

Hydrogel Sealant vs. Sutures to Prevent Postop Fluid Loss

Results from a multicenter study indicate that hydrogel sealant is safe and effective, and is better than sutures for the intraoperative management of clear corneal incisions with wound leakage as seen on Seidel testing, and for the prevention of postoperative fluid egress.

Healthy patients having uneventful clear corneal incision cataract surgery were recruited for this study at 24 ophthalmic clinical practices in the United States. Spontaneous and provoked fluid egress from wounds was evaluated at the time of surgery using a calibrated force gauge. Eyes with leakage were randomized to receive a hydrogel sealant (ReSure) or a nylon suture at the main incision site. Incision leakage was reevaluated one, three, seven and 28 days postoperatively.

Of 500 eyes, 488 had leakage at the time of cataract surgery. The leak was spontaneous in 244 cases (48.8 percent) and 488 (97.6 percent) of all incisions leaked with one ounce or less of applied force. After randomization, 12 (4.1 percent) of 295 eyes in the sealant group and 60 (34.1 percent) of 176 eyes in the suture group had wound leakage with provocation ($p<0.0001$). The overall incidence of adverse ocular events was statistically significantly lower in the sealant group than in the suture group ($p<0.05$).

Six of this article's authors are consultants to and shareholders of Ocular Therapeutix.

J Cataract Refract Surg 2014;40: 2057-2066.
Masket S, Hovanesian J, Levenson J, Tyson F, et al.

(continued from page 61)

status, there is a 1.8- to 4-percent rate of unexplained amblyopia in the United States, which may be due to transient phenomena that can temporarily occlude the visual axis (such as retinal, optic nerve and foveal hemorrhages). Fortunately, we will have two- and three-year follow-up on development of amblyopia in children identified with ocular abnormalities in the Newborn Eye Screen Testing (NEST) prospective study at Stanford University School of Medicine in the summers of 2015 and 2016, respectively.

Other strategies that are being employed are assessment of axial length, refraction, optical coherence studies of the macula, and, potentially, intraocular pressure assessment in the near future. While the NEST program is currently being evaluated as a prospective study with longitudinal follow-up with pediatric ophthalmology/retina specialists, it is evident from early data that commercialization and widespread adoption will be offered in the future.

The telemedicine experience in pediatric retinal diseases has been successful because it has avoided the pitfalls of casting too wide a net. Instead, we have identified niche markets with well-defined intervention points that are easily identified using the technology. These markets, whether in ROP or congenital ocular pathology, have a limited timeframe in which therapy is beneficial, but can result in life-long benefit. Therefore, the societal and patient benefit is large from these screening programs. As ophthalmologists, we need to continue to define very narrow ranges of targeted telemedicine screening that will offer immediate relief and benefit, while still maintaining economic feasibility. REVIEW

The telemedicine experience in pediatric retinal diseases has been successful because it has avoided the pitfalls of casting too wide a net.

Dr. Moshfeghi is an associate professor of ophthalmology at Stanford University School of Medicine where he is the director of the vitreoretinal surgery fellowship program and director of pediatric vitreoretinal surgery as well as director of telemedicine (ophthalmology). He may be reached at dariusm@stanford.edu.

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Confocal Scanning + True-Color Imaging

CenterVue announced Food and Drug Administration clearance for its Eidon true-color confocal scanner. The company calls Eidon the first fully automated retinal imaging system available in the global eye-care market that combines the advantages of confocal scanning with true-color imaging capabilities.

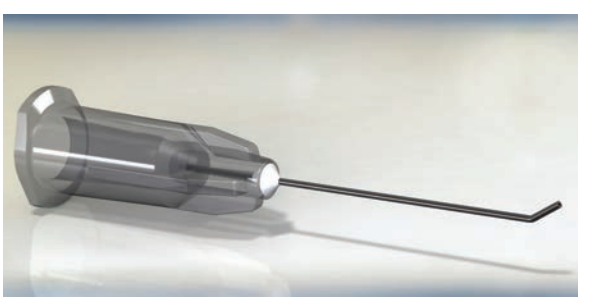
White-light, confocal imaging technology facilitates diagnosis and management of retinal disease, while the combination of confocal imaging and white light illumination provides greater contrast and superior image quality over a traditional fundus camera, says CenterVue. Further, the retinal appearance with Eidon's white-light source mirrors that seen during white-light, direct observational techniques. Eidon's optics allow imaging of the central retina as well as the periphery, over a viewing angle of up to 110 degrees. Multiple imaging modalities—true-color, red-free and infrared—provide information concerning different layers of the retina.

Eidon streamlines image acquisition and ensures minimum operator involvement by automatically aligning the patient's pupil, focusing on the retina and capturing images using a soft light source. The device can be used automatically or manually, with or without pupil dilation. It is operated via a dedicated software application as a standalone unit by means of a high-resolution, multi-touch tablet. For information, visit centervue.com.

Sterimedix: New Transzonular Injection Cannula

Sterimedix has introduced a new cannula for transzonular injections. Designed in conjunction with Jeffrey T. Liegner, MD, the cannula is designed for the intraoperative injection of steroid-antibiotic combinations at the end of a standard cataract procedure, which may replace the traditional patient-administered prophylaxis of antibiotic eye drops.

Available in 27 ga., the new cannula is angled with a 2-mm distal segment to facilitate safe and easy injection of the drug with minimal risk to the zonules and offers an easy approach to the delivery of medications to the desired site.



The cannula is supplied packed and sterile, in boxes of 10 pieces. Product code M2280.

Sterimedix manufactures a complete range of single-use products for ophthalmic surgery. For more information, visit sterimedix.com.

Catalys Laser Goes Mobile

ForTec Medical recently collaborated with Abbott's vision-care business to mobilize the Catalys Precision Laser System for the convenience of bringing this precision cataract procedure directly to ophthalmology practices across the United States.

ForTec notes the benefits of adopting Catalys Laser System in a mobile platform: "If your cataract surgical volume does not support the capital outlay, you can still leverage the finest laser cataract technology to meet your schedule. And if you do have higher surgical volumes and want to prove the value of the system prior to a purchase, you can leverage the mobile option while you ramp up your patient adoption."

ForTec Medical provides trained and credentialed technicians who expertly assist all scheduled procedures. For information, call 1 (800) 963-7101, or visit mobile catalys.com or fortecmedical.com. REVIEW

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Lid swelling and recent tearing and crusting of the eyelashes are the principal presenting signs for this middle-aged patient.

Alison Huggins, MD

Presentation

A 48-year-old African-American male presented with a two-month history of right upper lid swelling with recent-onset tearing and crusting of the eyelashes. He denied vision changes, diplopia, pain, history of trauma or recent illness. Systemic review of symptoms was negative for joint pain, shortness of breath, cough, abnormal bowel movements or urinary symptoms, but did reveal a recent rash on his upper and lower extremities for a week, with two days of facial skin involvement. He had initially presented to an outside hospital and had completed a course of oral cephalexin and topical bactroban without symptom resolution.

Medical History

The patient had no significant medical history, but did have a history of decreased color vision in both eyes. He denied tobacco, alcohol and intravenous drug abuse. He was not on any medications, and denied any known drug allergies.

Examination

The patient was afebrile with stable vital signs. His external examination demonstrated multiple crusted erythematous plaques on his face and neck. There was a soft, non-tender, mobile mass beneath the right upper lid with consequent mechanical and neurogenic right upper lid ptosis, demonstrated by decreased levator function. There was 2.5 mm of right hypoglobus. Hertel exophthalmometry revealed 5 mm of right-sided proptosis *(See Figure 1)*. There was no eyelid erythema or tenderness and no resistance to retropulsion.

The best-corrected visual acuity was 20/20 OU. Pupillary exam showed no anisocoria or relative afferent pupillary defect. A left hypertropia was present in primary gaze, and extraocular motility revealed only 50 percent supraduction of the right eye with proportionately vertical binocular diplopia in upgaze. Visual fields were full to confrontation in both eyes. Ishihara color plates were 5/8 in both eyes, and the patient said this was normal for him.

Anterior slit-lamp examination and fundoscopic examination were unrevealing with no signs of inflammation or infection. Intraocular pressures were 17 mmHg OU by Goldmann tonometry.

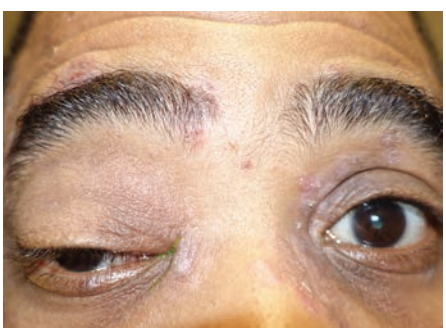

Figure 1. External photography demonstrating right orbital mass with associated ptosis, proptosis and hypoglobus, along with diffuse crusted, erythematous skin lesions.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 86

Diagnosis, Workup and Treatment

Given the presence of a painless, progressive superior orbital mass, the differential diagnosis included both inflammatory and neoplastic processes. Laboratory studies for autoimmune, infectious and infiltrative processes (Lyme, ACE, C-ANCA, P-ANCA, FTA-Ab, ANA, HIV, RF, C3, C4, CRP, ESR and CBC with differential) were completed and all unremarkable, with the exception of C-reactive protein of 6 (normal 0 to 5) and ESR of 20 (normal 0 to 10). The patient also had a normal chest radiograph. An MRI of the brain and orbits with intravenous contrast was obtained to further characterize the right orbital mass. Imaging revealed a superior diffuse right orbital mass *(See Figure 2)*.

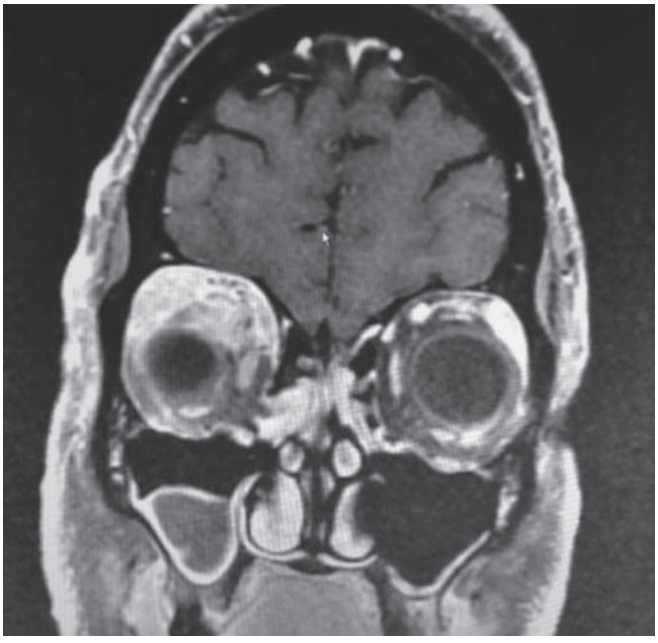

Figure 2. A mildly heterogeneously enhancing mass occupying the superior extraconal space of the right orbit.

On follow-up, the patient's exam remained stable. His lab workup was negative, although it consisted of tests with generally poor sensitivity for orbitally limited diseases. Therefore, given his unrevealing laboratory studies and concerning clinical exam and imaging, the differential diagnosis remained broad and included poorly circumscribed lesions, such as idiopathic inflammation; specific inflammatory conditions (sarcoid, Wegener's, Sjögren's, etc.); metastatic lesions; lymphoproliferative disease; and vascular lesions. The concern for a neoplastic etiology and unclear diagnosis prompted orbitotomy with lesion biopsy and mass debulking though a lid crease approach. Fresh tissue was sent for flow cytometry, which showed no evidence of lymphoproliferative disease. However, the histopathology demonstrated non-caseating granulomatous inflammation consistent with sarcoidosis *(See Figure 3)*.

Prior to the initiation of prednisone, the patient underwent a computerized tomography scan of the chest that demonstrated hilar lymphadenopathy and interstitial inflammation, concerning for pulmonary sarcoid. Quantiferon Gold antibody testing ruled out tuberculosis. Referral to pulmonology demonstrated normal pulmonary function testing and dermatology referral led to a biopsy of the patient's facial rash. This revealed psoriasiform dermatitis without granulomatous inflammation. The patient was also referred to rheumatology for definitive therapy.

While rheumatology input was pending, the patient was diagnosed with sarcoidosis and started on 60mg daily of oral prednisone. He had significant improvement following surgical debulking and corticosteroids. Two weeks postop, his proptosis, hypoglobus and extra ocular motility had improved *(See Figure 4)*. There was persistent right upper lid ptosis. Over two months time, he tolerated an oral prednisone taper to 5 mg daily, and is awaiting evaluation by his rheumatologist to determine the need for long-term immunosuppression.

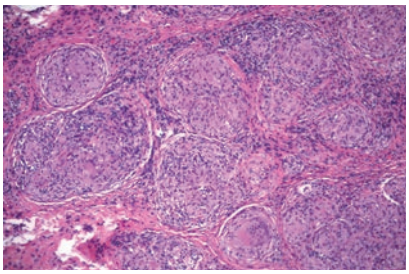

Figure 3. Hematoxylin and eosin stain of superior orbital mass histologic specimen demonstrating non-caseating granulomatous inflammation.

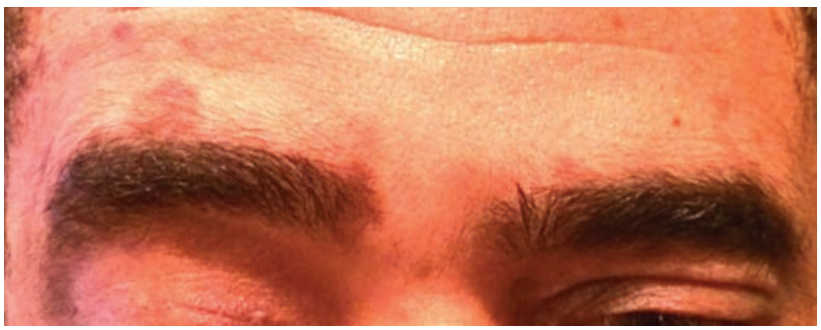

Figure 4. Two weeks postop: persistent ptosis but improved right proptosis, as well as improvement of previously present erythematous skin lesions.

Discussion

Sarcoidosis is a multi-system disease of non-caseating granulomatous inflammation thought to be the result of immune stimulation by self or non-self antigens.[1] Despite investigation of potential etiologies, including a multitude of genetic, infectious and environmental factors, there have been no established causative relationships. Regardless of the inciting antigen, the final common pathway of disease is thought to result from an exaggerated immune response resulting in a T helper cell 1 immune cascade with the subsequent elaboration of chemokines and cytokines, resulting in organ fibrosis and dysfunction.[1]

Variability in the severity and type of disease manifestations has made quantifying disease frequency challenging, as it can have a subclinical course in some. Despite this, there is a predilection for certain races and ethnicities; specifically, it is most commonly seen among African Americans, as well as Caucasians of Scandinavian and Irish decent.[2] The incidence of sarcoidosis among African Americans is 35 to 80 per 100,000 with a 30-percent higher risk in females and a peak incidence in the third to fourth decade of life. Among Northern Europeans, the incidence is 15 to 20 in 100,000, they share a similar increased risk in females and age of onset to the African-American population.[3]

Pulmonary involvement is most common among patients with sarcoidosis, occurring in more than 90 percent of patients with sarcoidosis.[1] However, this disease also frequently manifests in the lymph nodes, skin and eyes.[4] A comprehensive review of the clinical features of sarcoidosis discusses the dermatologic disease manifestations as two discrete classifications: nonspecific lesions that are inflammatory skin reactions, most commonly erythema nodosum; and specific lesions that demonstrate granulomatous inflammation on biopsy. Specific lesions are commonly firm, 2- to 5-mm papules that are translucent red-brown or yellow-brown in color; however appearance is very variable[4] and may include plaques, psoriaform lesions and intradermal nodules, among others. Lupus pernio is a disfiguring form of facial sarcoidosis that may be severe enough to erode into bone. Interestingly, skin lesions have a predilection for involvement of scars, tattoos, skin piercings and sites of old trauma.[4] In this case, psoriaform dermatitis was present, but there was no evidence of granulomatous inflammation to suggest this rash was a specific lesion of sarcoidosis.

The most common ophthalmologic manifestation of sarcoid is uveitis, present in 70 percent of patients with ocular involvement.

The most common ophthalmologic manifestation of sarcoid is uveitis, present in 70 percent of patients with ocular involvement.[1] Orbital involvement is much rarer; in a review of 379 cases of ocular sarcoidosis at Henry Ford Hospital, only 30 cases demonstrated orbital and/or adnexal involvement. Of these, only nine cases involved the orbit, eyelids and extraocular muscles.[4] The majority of orbital lesions were situated in an anterior, superior position, as seen in this case.

Interestingly, in this case the patient had disease manifestations in all three of the aforementioned organ systems at the time of diagnosis. It is unclear from the current literature how frequently patients present with pulmonary, dermatologic and ocular findings simultaneously. Given the reported frequency of each organ system's involvement, the incidence of all three occurring likely ranges from 1 to 23 percent of patients.[4] Nonetheless, a large case-control study investigating the clinical characteristics of patients with newly diagnosed sarcoidosis illustrated that it is relatively rare for patients to present with disease in three organ systems. Among the 736 studied patients, only 13 percent had disease involving three organ systems at the time of diagnosis.[5]

On the other hand, 50 percent of patients will have single-organ involvement at presentation.[5] In fact, ocular sarcoid may pose a diagnostic dilemma, as it is not uncommon for the systemic and laboratory workup to be unrevealing. Short of biopsy, no clear diagnostic criteria for definitive diagnosis have been established. In cases of systemic involvement, chest radiography demonstrating hilar adenopathy and an elevated ACE level are suggestive of sarcoidosis. However, CT scan of the chest has been found to have increased diagnostic sensitivity.[4]

The mainstay of therapy for sarcoidosis remains immunosuppression with corticosteroids.[1] However, in the aforementioned review of patients with orbital sarcoid, surgical debulking is also used to supplement systemic therapy with good long-term outcomes.[6] At present, there are no randomized controlled trials comparing therapeutic treatment options in systemic sarcoidosis; however, steroid-sparing immunosuppressants are widely used. Monoclonal antibodies used to antagonize tumor-necrosis factor alpha, a key player in the sarcoidosis inflammatory cascade, have shown benefit in refractory cases. While none of these treatment modalities are without risk, the question of whether or not to pursue surgical intervention in this steroid-re-

sponsive condition remains unclear. For patients undergoing surgery for diagnosis, as in this case, debulking at this time certainly seems appropriate. However, for patients with more classic disease manifestations, surgery for the purpose of debulking may not be indicated before a trial of immunosuppression.

In conclusion, ocular sarcoidosis remains a great masquerader in ophthalmologic disease given its diverse manifestations, and should be considered in cases when inflammatory and infiltrative diagnoses are considered. Likewise, clinical suspicion should remain high despite initial unremarkable ACE level and chest radiography as, in this case, these tests are often negative in ophthalmologic disease. Additionally, the threshold for checking a CT scan of the chest should be low, as it is a more sensitive test than an X-ray. Sarcoidosis responds well to systemic immunosuppressive therapy, but care must be taken to rule out all possible neoplastic and infectious etiologies prior to trial of systemic immunosuppression. Further, consultation of a rheumatologist should be sought to entertain initiation of steroid-sparing agents and for evaluation and treatment of systemic disease. REVIEW

The author would like to give special thanks and acknowledgement to Brian Doyle, MD, Ralph C. Eagle, MD, and Michael P. Rabinowitz, MD.

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REVIEW Advertising Index

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LUMIGAN® 0.01%
(bimatoprost ophthalmic solution)

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

INDICATIONS AND USAGE

LUMIGAN® (bimatoprost ophthalmic solution) 0.01% 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®** (bimatoprost ophthalmic solution) 0.01% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17.1)]*.

Eyelash Changes: LUMIGAN® 0.01% 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: Prostaglandin analogs, including bimatoprost, have been reported to cause intraocular inflammation. In addition, because these products may exacerbate inflammation, caution should be used in patients with active intraocular inflammation (e.g., uveitis).

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% 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.

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 *[see Patient Counseling Information (17.3)]*.

Use with Contact Lenses: Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% 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 a 12-month clinical study with bimatoprost ophthalmic solutions 0.01%, the most common adverse reaction was conjunctival hyperemia (31%). Approximately 1.6% of patients discontinued therapy due to conjunctival hyperemia. Other adverse drug reactions (reported in 1 to 4% of patients) with **LUMIGAN®** 0.01% in this study included conjunctival edema, conjunctival hemorrhage, eye irritation, eye pain, eye pruritus, erythema of eyelid, eyelids pruritus, growth of eyelashes, hypertrichosis, instillation site irritation, punctate keratitis, skin hyperpigmentation, vision blurred, and visual acuity reduced.

Postmarketing Experience: The following reaction has been identified during postmarketing use of **LUMIGAN®** 0.01% in clinical practice. Because it was reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reaction, which has been chosen for inclusion due to either its seriousness, frequency of reporting, possible causal connection to **LUMIGAN®** 0.01%, or a combination of these factors, includes headache.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

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®** (bimatoprost ophthalmic solution) 0.01% administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** 0.01% 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% 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®** 0.01% 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®** (bimatoprost ophthalmic solution) 0.01% 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/m^2 is at least 210 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.01% 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: Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Also inform patients about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.01%.

Potential for Eyelash Changes: Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** 0.01%. 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: Instruct patients 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: Advise patients 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%.

Use with Contact Lenses: Advise patients that **LUMIGAN®** 0.01% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% and may be reinserted 15 minutes following its administration.

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

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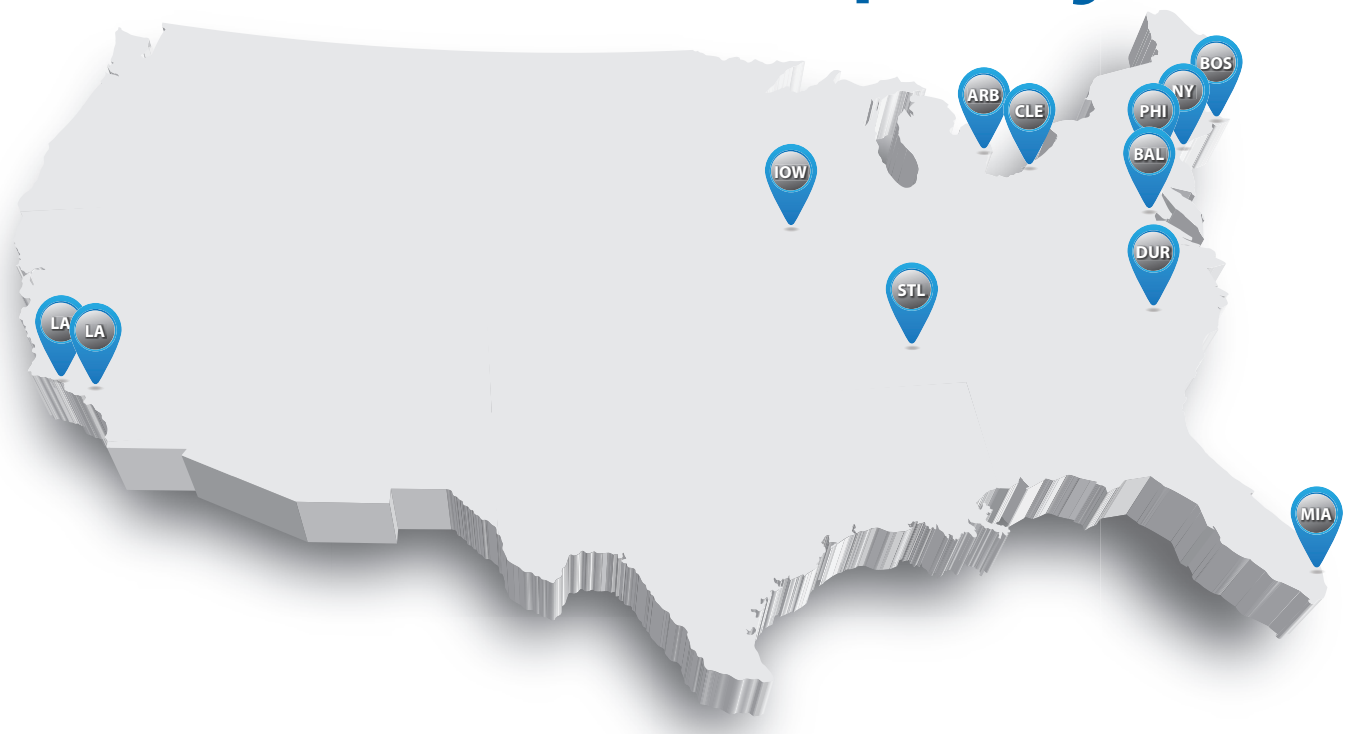

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INDICATION

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® 0.01% causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® 0.01% 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.

Prostaglandin analogs, including bimatoprost, have been reported to cause intraocular inflammation. These products may also exacerbate inflammation, so use with caution in patients with active intraocular inflammation (e.g., uveitis). Macular edema, including cystoid macular edema, has been reported with LUMIGAN® 0.01%. LUMIGAN® 0.01% 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. Remove contact lenses prior to instillation of LUMIGAN® 0.01% and reinsert after 15 minutes.

ADVERSE REACTIONS

The most common adverse reaction was conjunctival hyperemia (31%). Approximately 1.6% of patients discontinued therapy due to conjunctival hyperemia. Other adverse drug reactions (reported in 1 to 4% of patients) with LUMIGAN® 0.01% included conjunctival edema, conjunctival hemorrhage, eye irritation, eye pain, eye pruritus, erythema of eyelid, eyelids pruritus, growth of eyelashes, hypertrichosis, instillation site irritation, punctate keratitis, skin hyperpigmentation, vision blurred, and visual acuity reduced.

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

1. LUMIGAN® Prescribing Information. **2.** Katz LJ, Cohen JS, Batoosingh AL, Felix C, Shu V, Schiffman RM. Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol.* 2010;149(4):661-671. **3.** Managed Markets Insight & Technology, LLC, database, as of October 2014.

LUMIGAN® 0.01%
(bimatoprost ophthalmic solution) 0.01%

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