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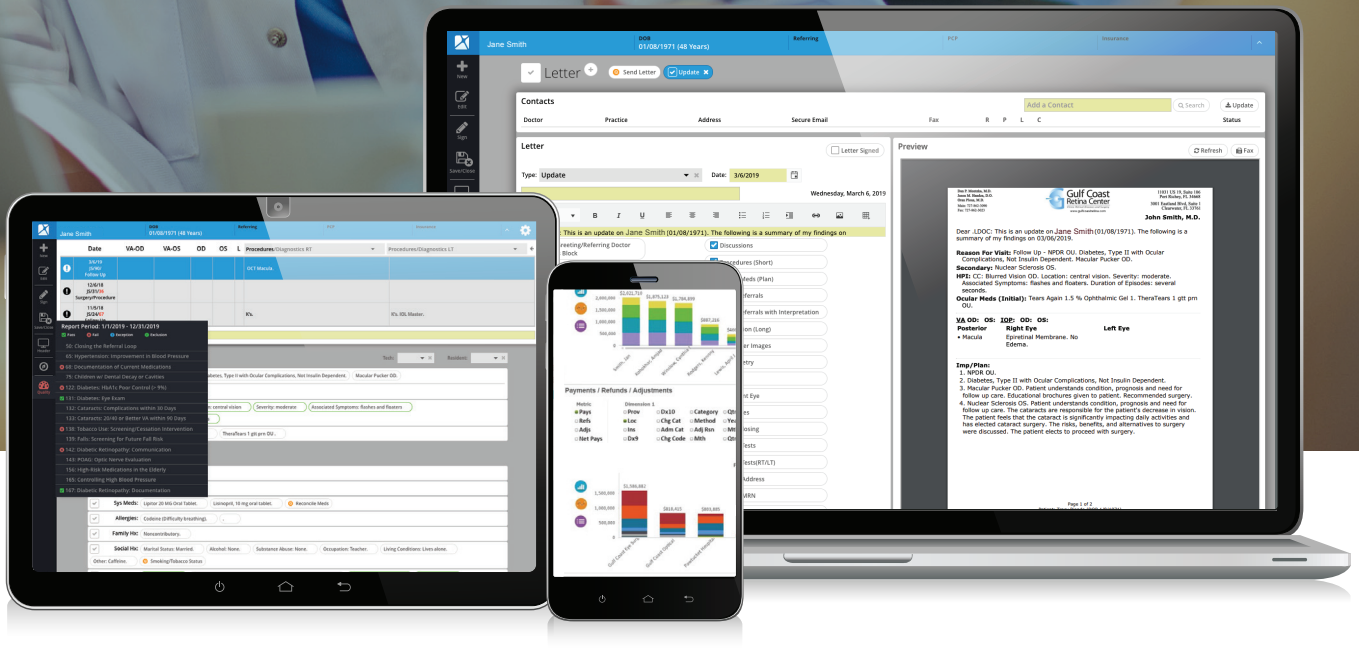

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References: 1. McAlinden C. An overview of thyroid eye disease. *Eye Vis.* 2014;1:9. doi:10.1186/s40662-014-0009-8. **2.** Weiler DL. Thyroid eye disease: a review. *Clin Exp Optom.* 2017;100:20-25. **3.** Verity DH, Rose GE. Acute thyroid eye disease (TED): principles of medical and surgical management. *Eye (Lond).* 2013;27:308-319. doi:10.1038/eye.2012.284. **4.** Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management. *J Ophthalmol.* 2015;2015:249125. doi:10.1155/2015/249125. **5.** Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J.* 2016;5:9-26. doi:10.1159/000443828.

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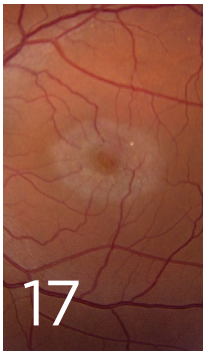

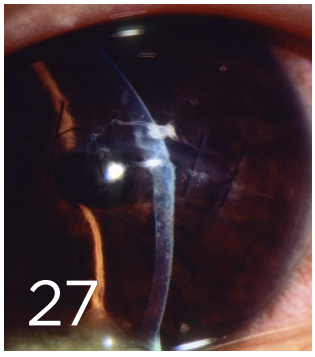

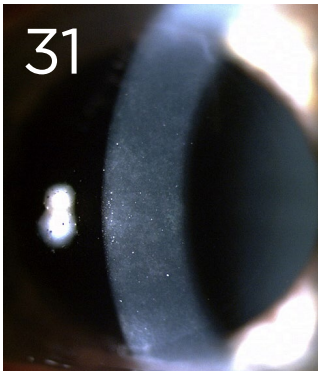

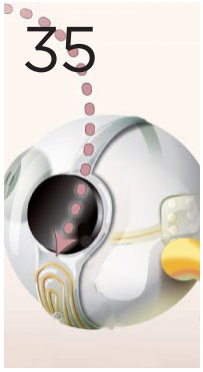

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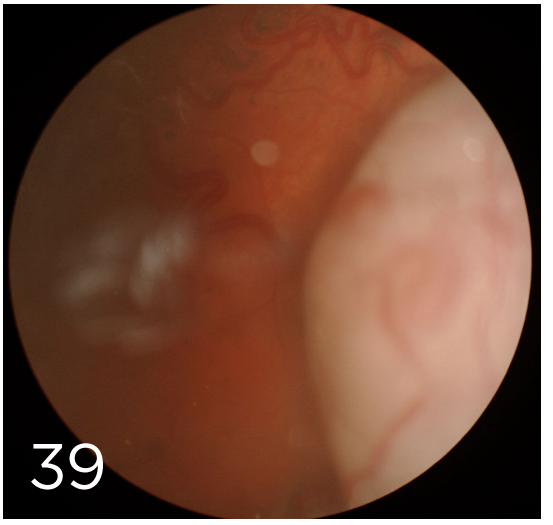

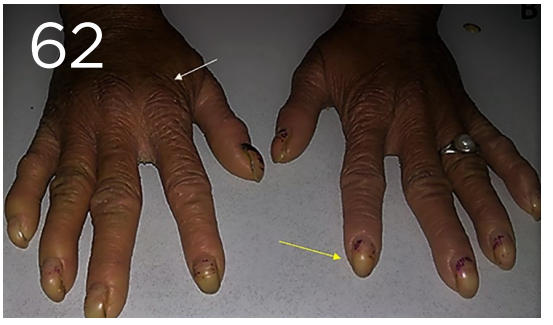

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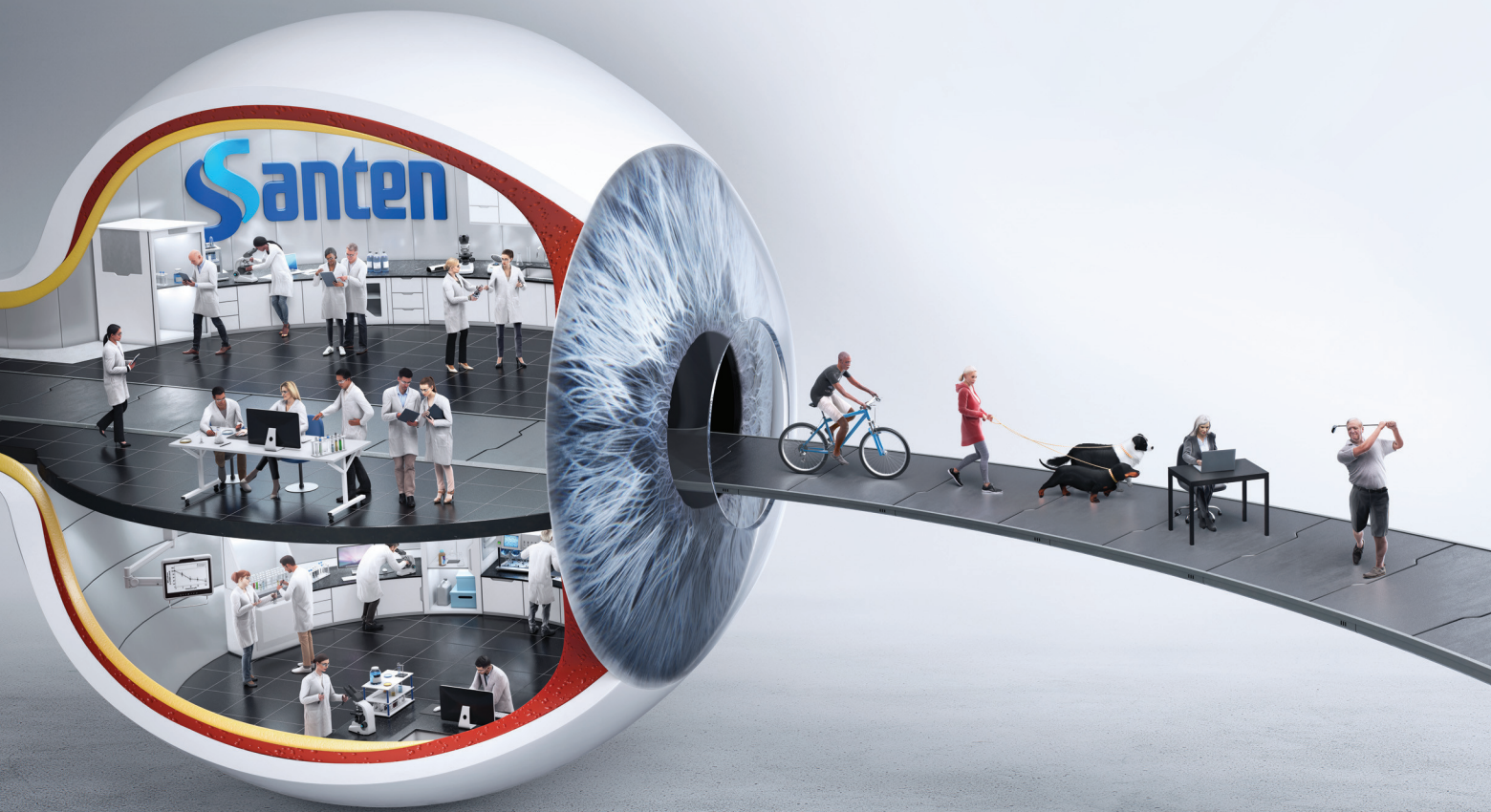

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ILEVRO® (nepafenac ophthalmic suspension) 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

Dosage and Administration
One drop of ILEVRO® 0.3% should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

IMPORTANT SAFETY INFORMATION

Contraindications
ILEVRO® 0.3% is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other nonsteroidal anti-inflammatory drugs (NSAIDs).

Warnings and Precautions
- *Increased Bleeding Time* – With some NSAIDs, including ILEVRO® 0.3%, there exists the potential for increased bleeding time. Ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- *Delayed Healing* – Topical NSAIDs, including ILEVRO® 0.3%, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- *Corneal Effects* – Use of topical NSAIDs may result in keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including ILEVRO® 0.3%, and should be closely monitored for corneal health.

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

  Use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.
- *Contact Lens Wear* – ILEVRO® 0.3% should not be administered while using contact lenses.

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

For additional information about ILEVRO® 0.3%, please refer to the Brief Summary of Prescribing Information on the adjacent page.

Terms and Conditions: Limitations apply. Eligible, commercially insured patients may pay as little as $15 in out-of-pocket expenses for each 3-mL or 1.7-mL bottle of ILEVRO® 0.3%, with a maximum benefit per bottle of $285. **This offer is not valid under Medicare, Medicaid, or any other federal or state program.** See additional terms and conditions at www.copay.novartispharma.com.

†*Study Design:* Results from 2 randomized, multicenter, controlled, double-masked trials of adult patients undergoing cataract extraction. In Study 1, patients were randomized to receive either ILEVRO® Suspension (n=851), NEVANAC® Suspension (n=845), ILEVRO® Suspension vehicle (n=211), or NEVANAC® Suspension vehicle (n=213). In Study 2, patients were randomized to receive either ILEVRO® Suspension (n=540) or ILEVRO® Suspension vehicle (n=268).[2,3]

‡61% to 65% with ILEVRO® Suspension versus 24% to 32% with vehicle; $P<0.05$.

§84% to 86% with ILEVRO® Suspension versus 38% to 46% with vehicle; $P<0.05$.

References: 1. Data on file. IMS Health. 2. Ilevro [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2019. 3. Data on file. Novartis Pharmaceuticals Corporation; 2011. 4. BromSite (bromfenac ophthalmic solution) 0.075% [package insert]. Cranbury, NJ: Sun Pharma Global FZE; 2016. 5. Prolensa (bromfenac ophthalmic solution) 0.07% [prescribing information]. Bridgewater, NJ: Bausch & Lomb; 2016. 6. Nevanac (nepafenac ophthalmic suspension) 0.1% [package insert]. Fort Worth, TX: Alcon Laboratories Inc; 2017.

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ILEVRO* (nepafenac ophthalmic suspension) 0.3%, topical ophthalmic
Initial U.S. Approval: 2005

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

ILEVRO* 0.3% is indicated for the treatment of pain and inflammation associated with cataract surgery.

4 CONTRAINDICATIONS

ILEVRO* 0.3% is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other non-steroidal anti-inflammatory drugs (NSAIDs).

5 WARNINGS AND PRECAUTIONS

5.1 Increased Bleeding Time

With some NSAIDS including ILEVRO* 0.3%, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.

It is recommended that ILEVRO* 0.3% be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.2 Delayed Healing

Topical NSAIDs including ILEVRO* 0.3%, 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.

5.3 Corneal Effects

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO* 0.3% and should be closely monitored for corneal health.

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

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

5.4 Contact Lens Wear

ILEVRO* 0.3% should not be administered while using contact lenses.

6 ADVERSE REACTIONS

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

6.1 Serious and Otherwise Important Adverse Reactions

The following adverse reactions are discussed in greater detail in other sections of labeling.

- Increased Bleeding Time *[see Warnings and Precautions (5.1)]*
- Delayed Healing *[see Warnings and Precautions (5.2)]*
- Corneal Effects *[see Warnings and Precautions (5.3)]*

6.2 Ocular Adverse Reactions

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

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

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

6.3 Non-Ocular Adverse Reactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects.

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

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO* 0.3% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects

Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO* 0.3% during late pregnancy should be avoided.

8.3 Nursing Mothers

Nepafenac is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO* 0.3% is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of ILEVRO* 0.3% in pediatric patients below the age of 10 years have not been established.

8.5 Geriatric Use

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

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Opinion

RUTH D. WILLIAMS, MD

In Defense of Work-Life *Im*balance

Work-life balance is a popular topic of conversation among young physicians. On one hand, it's terrific that ophthalmologists—male and female—have the freedom to discuss the challenges of integrating family priorities, patient care, career goals, self-care, and leisure. But I must admit that I hate the actual phrase.

To begin with, it doesn't reflect reality. Our endeavors are far too complex to be described as a balancing act. Work-life balance implies that there is some magical place of harmony where one has devoted just the right amount of attention to career and to the rest of life. I imagine a teeter-totter that is weighted on one side with ophthalmology and on the other side with my spouse and three kids (and exercise, vacation, friends, reading, and entertaining), but it's erratically bouncing up and down. This isn't a metaphor that works for me.

I'm also bothered by the implication that work doesn't count as real life. On the contrary, our work is one of the most meaningful aspects of our lives! It has a concrete purpose: to preserve and restore vision and to show compassion to our patients. And there's more. Because most of us spend more time at work than at home, our relationships with colleagues, employees, and patients can have the richness and complexity of familial ties. After 28 years of practice, I think of my colleagues as brothers and sisters. So, work doesn't pull me away from my family; it's an aspect of family. (In my case this is literally true, as my husband and his uncle are ophthalmologists in our practice.)

In lieu of a teeter-totter, I imagine a web that is composed of my children, husband, sports, ophthalmic practice, colleagues, and friends. Ophthalmology doesn't steal from my other commitments; all of the strands are vital. And when one portion of life causes disappointment or stress, other aspects provide comfort, joy, and meaning. Also, not all career arcs have the same shape, since some might choose to devote more attention to other priorities—such as young children—for a period of time. There is an ebb and flow to the commitments.

Still, patient care and professional development require much from us. It's dishonest to pretend that the rewards of a demanding career, no matter how wonderful, always compensate for the stress that it generates—or that work doesn't take something away from our families. We are always making decisions about which priority takes precedence, and it's hard to know if we've made the right choice—or if there even *is* a right choice.

I frequently hear younger ophthalmologists mention the guilt triggered by being away from their children or, conversely, by taking a day off from work or study for play. While guilt can be useful if it causes us to reassess choices, mostly it's a waste of energy.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Regret, however, can be of value. Despite our best efforts, we won't always get it right—and although it's a hard lesson to learn, I've come to realize that mistakes are okay. My son (now 21) was a fifth grader when a classmate of his died. I had a few hours to decide whether to board the plane to attend an Academy board meeting or to stay home and attend the funeral. I went to the meeting, and my husband went to the funeral with our son.

To this day, I wish I had been at the funeral. I've apologized to my son since, and it's sparked an ongoing dialogue about his friend and her importance in his life. My regret has turned out to be an opportunity for deepening our relationship, because it showed my son how much I care and how much I try to make wise choices.

In third grade, this same son dressed as Mahatma Gandhi for Living History Day. The night before, he asked me to shave his head so he'd really look like Gandhi. He was "all in." This story illustrates my personal approach to work-life balance: Don't waste energy on guilt. Instead, embrace the task of the hour, with your full attention and commitment.

Life as a physician-parent-spouse-friend is wholehearted and difficult and joyful and meaningful and full of big love. But it's never quite balanced.

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Current Perspective

DAVID W. PARKE II, MD

The Academy and Optometry

Your Academy is about to undertake something it has *never* previously attempted on any issue—a survey of its entire U.S. membership on an important policy issue. Your participation is vital. The purpose of this column is to introduce the survey and to frame the questions.

Patient Safety Is Paramount

For many ophthalmologists there are very few professional issues that elicit such a strong emotional reaction as our relationship with optometry. At the community level, both professions frequently work together collaboratively in service to patients. But at the state level, legislative scope of practice battles between ophthalmology and optometry have been a fact of life for both professions for over 50 years. In recent years optometric state societies have introduced 15-20 bills annually to legislatively expand their scopes of practice, and I estimate that both sides expend (in addition to thousands of hours of time taken away from practice) about $20 million to $25 million each year on lobbying and related expenses.

Most ophthalmologists believe that these battles center on a core principle—that the privilege and responsibility to provide complex medical and surgical eye care should be based on education, experience, and demonstrated competence rather than upon lobbying, donations, and legislative fiat. This is an issue of patient safety and professionalism. The Academy holds this principle dear, and we believe it is in our patients' best interest not to compromise that principle.

Our defense of that principle, however, does not necessarily imply that the professions should be forever in conflict on all questions with regard to the best care of patients.

Many Members Work With ODs

The practice of ophthalmology and of optometry are embedded in an evolving landscape of demographic trends, delivery structures, and economics. How, for example, should ophthalmology provide appropriate access to care for a rapidly growing and aging population? Ophthalmology, like every specialty in medicine, understands that delivery of optimal patient care is a team endeavor. Over 50% of ophthalmologists work in a practice that employs optometrists. Additionally, nearly every practice avails itself of the skills of other professionals including a mix of opticians, technicians, practice executives, nurses, orthoptists, imaging specialists, and IT experts. We are more efficient and effective working collaboratively than individually. In the operating room (with an entirely different team) all operating team members are empowered to call a timeout if there is a question as to which IOL or which medication should be employed. We, and particularly the patients, are all safer because of it.

The Academy itself has evolved during this same period. What started in 1896 as an organization dedicated to the education of only practicing ophthalmologists now includes residents, fellows, and membership categories for scientists, practice executives, and nurses—and has for years. Its Annual Meeting offers courses for all of these groups, including hundreds of offerings for ophthalmologists.

David W. Parke II, MD
Academy CEO

In recent years, there have been some requests from ophthalmologist members for the Academy to explore options to include educational venues for optometrists—particularly those optometrists who are in ophthalmologists' practices. These members basically have said, "I would rather have my society educate all the members of my team." These requests have arisen at the grassroots level from both individual members of the Academy and from individual state societies. There have also been recommendations from members that the Academy consider finding a place for these optometrists in the Academy's structure—much as exists for other members of the eye care team.

The Perspectives

There have been strong and articulate voices on both sides of these requests. Those in support note the demographic imperative to work together to meet the needs of a growing

and aging population that is not matched by a similar growth in the number of ophthalmologists. They also say that there is a broad base of support for team-based education, and they note the high quality of Annual Meeting education programs. They recognize the positive relationships between individual ophthalmologists and optometrists in providing patient care and the desirability of breaking down barriers wherever possible, albeit consistent with our patient care principles (such as teaching surgical procedures only to ophthalmologists).

Those opposed note the challenges in overcoming decades of mutual scope of practice–generated animosities, the fact that the Academy is an "ophthalmology society," that Academy training has in the past been and might in the future be legislatively misrepresented by some optometrists and risk patient harm, and that it might "blur the lines of education and perceived competency" between the two professions. Some believe that, given the differences in training, it is impossible to provide a meaningful educational interface without compromising core quality of care and patient safety principles.

There is no predetermined plan of action. The objective is to engage the profession in a careful, deliberate discussion, and then to know, for the first time, what the membership really thinks and prefers. This will then guide where we go from here.

And there are other considerations—both pro and con.

Why We Need a Survey

The issues have been discussed by the Academy Board of Trustees, by the Academy Council, and by state leaderships off and on for years—and intensively over the past six months. All generally agree that a) it is a highly charged and important issue, and b) no one actually knows what the 18,000+ practicing ophthalmologists in the United States truly think about it.

Accordingly, we will all find out. In early January, the Academy will conduct a first-ever survey of its entire domestic practicing membership. It is an opinion survey, not a formal vote on an issue. The survey results will be made available to all members in early 2020. And the outcome will help guide policy as the profession and patient care advance.

A couple of things are worth noting and emphasizing. First, this discussion and this survey are not linked to any proposed change in advocacy principles or in the intensity with which these principles will be defended. The Academy remains vigorously committed to scope of clinical practice defined by education, experience, and demonstrated clinical competence.

Second, there is no predetermined plan of action. The objective is to engage the profession in a careful, deliberate discussion, and then to know, for the first time, what the membership really thinks and prefers. This will then guide where we go from here. And change should be consensus-driven. In many respects, the outcome of the survey may be less important than the process itself in clarifying the core issues of concern, raising unrecognized questions, and guiding the next steps. A member wrote to me on this subject and commented that her father always noted, "It's the debate and discussion that are important."

There has been increasing cooperation in some arenas between optometry and ophthalmology in recent years. We have worked together on policy statements pertaining to common ground issues such as cosmetic contact lenses. We have delivered joint educational symposia on topics such as dry eye, myopia prevention, and amblyopia. We have advocated together for payment for vision rehabilitation services for those in need, for early drop refills, prohibiting scleral tattoos, and other patient protections.

Regarding the Academy and optometry, the questions now are, "Should there be next steps and, if so, what should they be?" The potential options are not binary ones. They will be nuanced. And some may be better implemented at local or state levels than at the national one. Regardless, patient needs must remain front and center. The process for meeting these needs should be determined and led by physicians—not by politicians and policy wonks.

It is possible that, based in part on the survey responses, this profession-wide reexamination will lead to no change in Academy policies and procedures. If so, it is much better that we arrive at the decision based on careful deliberation of the alternatives, rather than unwillingness to consider alternatives. Again, the process itself has great value. It is how we as medical professionals make patient care decisions—obtaining and considering all available data.

Your Opinion Is Critical

The survey questions are being formulated by an independent professional firm in conjunction with a group of colleagues randomly chosen from state leadership to help ensure that it is as free of bias as possible. The survey will be administered by an independent survey firm. It will appear in your inbox in early January with announcements in *Academy Express* and *Washington Report Express*. Please fill it out. Your opinion is critical, and by participating you have the direct opportunity to impact your Academy's direction.

In the meantime, I encourage Academy members to go to aao.org/eyenet/article/the-academy-and-optometry, read perspectives from your colleagues, and post your own view.

Thank you and Happy Holidays.

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Julia A. Haller, MD, Ophthalmologist-in-Chief

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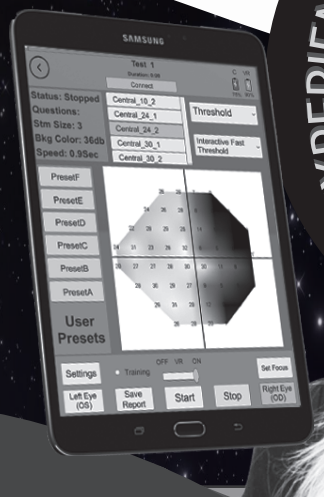

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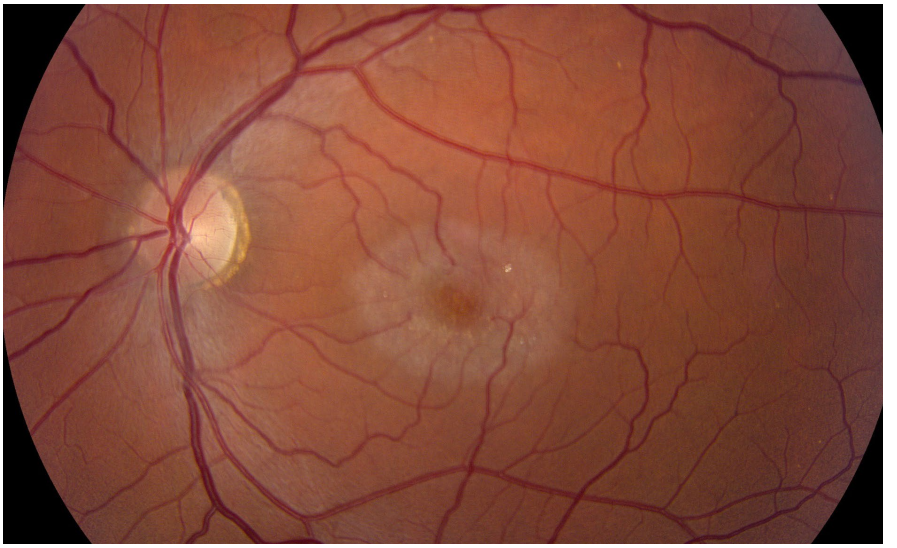


COMPLEX INTERACTION. *The researchers cautioned against prescribing fenofibrate or serine supplements to patients with MacTel type 2, "given the complex genetic etiology of the condition and the genetic diversity in the patient population."*

Jason S. Calhoun, COA

RETINA

Metabolic Link to MacTel Confirmed

AN INTERNATIONAL RESEARCH collaboration has discovered that a deficiency of the amino acid serine is associated with the accumulation of certain toxic lipids in the blood and retina, causing photoreceptor apoptosis in macular telangiectasia (MacTel) type 2.[1]

The new finding about this orphan disease points researchers toward a possible molecular road map for slowing or preventing retinal degeneration in MacTel, said Martin Friedlander, MD, PhD, at Lowy Medical Research Institute in La Jolla, California. "Through this highly collaborative project, we now have an understanding of macular telangiectasia. If you see a patient with MacTel, you should tell them that new research has revealed a cause of the disease and that we might have a treatment in the next few years," said Dr. Friedlander, also at Scripps Research and Scripps Clinic in La Jolla.

Building the case. In 2017, the MacTel research group first reported on the suspected retinal role of serine,[2] which is used in many pathways in the body but was not previously known to affect macular health.

In the current study, the researchers confirmed the link, and they determined that low serine levels lead to the same lipid-associated degenerative process that occurs in a rare genetic disease called hereditary sensory and autonomic neuropathy 1 (HSAN1).[1] Moreover, they identified the gene common to both MacTel and HSAN1, although this genetic variant is found in only a small number of MacTel patients, Dr. Friedlander said.

Tracking toxicity. Through a painstaking combination of genetic analysis, metabolomics, animal studies, and in vitro tests in human retinal organoids grown from stem cells, the scientists determined that insufficient serine leads to the formation of toxic deoxysphingolipids in the retina. These toxic molecules form instead of normal sphingolipids when serine is lacking, Dr. Friedlander said.

When the researchers examined 13 HSAN1 patients who had not previously had ophthalmic testing, nine had undiagnosed MacTel, and two more had early signs of the disease. Furthermore, blood tests in 125 MacTel patients showed levels of deoxysphingolipids 84.2% higher than those found in unaffected controls.

A new disease class? "In this case, a single biochemical mechanism causes disease in both the eye and the peripheral nervous system," Dr. Friedlander said. "We think this is an example of a new class of neurodegenerative disease that we are calling 'serineopathies.'" He added that the finding may have application to more common metabolic and neurological disorders. For instance, he noted, elevated blood levels of deoxysphingolipids have been reported in people with diabetic retinopathy.[3]

Patient management. The MacTel researchers found that cell damage was prevented if the scientists either supplemented with serine or used a drug that regulates lipid metabolism to block the toxic lipids from forming, Dr. Friedlander said. (For this study, they used fenofibrate.)

Already, some physicians are treating HSAN1 patients with oral serine supplements, Dr. Friedlander said. But it is too early to recommend this for patients who have MacTel or are at genetic risk for it, he said. For now, he recommended that patients whose neuropathy has been diagnosed as HSAN1

be examined for signs of macular telangiectasia. —*Linda Roach*

1 Ganter ML et al. *N Engl J* Med. 2019;381(15):1422-1433.
2 Scerri TS et al. *Nat Genet.* 2017;49(4):559-567.
3 Zuellig RA et al. *Diabetes.* 2014;63(4):1326-1329.
Relevant financial disclosures—Dr. Friedlander: None.

GLAUCOMA

Gabapentin Raises Risk of Acute Angle Closure

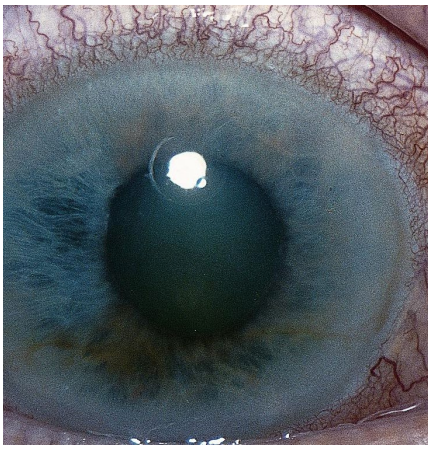
THE GABAPENTINOIDS GABAPENTIN and pregabalin are among the most commonly prescribed drugs in North America. Now, researchers have found an association between gabapentin and the incidence of acute angle-closure glaucoma (AAG).[1] A similar association was not found for pregabalin.

Both drugs are approved to treat epilepsy and selected chronic pain conditions and are widely used off-label for mood disorders and pain.[2] "We were surprised that this commonly prescribed psychotropic agent might increase the risk of AAG," said coauthor Mahyar Etminan, PharmD, MSc, at the University of British Columbia Eye Care Center in Vancouver, British Columbia, Canada.

The bottom line, he said: "If you see patients with acute angle-closure glaucoma and they are on gabapentin, this drug might be the culprit."

Study rationale. Previously, gabapentin has been linked to AAG, but only in case reports citing complaints of blurred vision, nystagmus, diplopia, and visual defects. These reports, plus the wide use of the drug, factored into the decision to conduct a large epidemiological study, Dr. Etminan said.

Study specifics. Researchers evaluated a random sample of 1,307 patients who developed AAG after gabapentin and pregabalin exposure in the year before diagnosis. The sample, drawn from a medical and pharmaceutical claims database over a 10-year period ending Dec. 31, 2016, also included 13,070 controls.



RX LINK. *Additional evidence has emerged of a link between acute angle-closure glaucoma (shown here) and gabapentin use.*

Who's at risk? Gabapentin use in the year before AAG diagnosis was associ-

COMPREHENSIVE

RVO Risk: CVD and Hypertension

RETINAL VEIN OCCLUSION (RVO) IS ASSOCIATED WITH increased risks for stroke, myocardial infarction (MI), and other cardiovascular events, conferring levels of risk beyond traditional factors, a meta-analysis of 15 longitudinal cohort studies has concluded.[1]

Meanwhile, a separate meta-analysis has found that hypertension doubles the risk of RVO, making it the strongest risk factor for development of an occluded retinal vein.[2]

CVD in general. Researchers in New York and Hawaii evaluated observational data on 474,466 subjects, 60,069 of whom (12.7%) had RVO. The results showed that the patients with RVO were at greater risk of cardiovascular disease (CVD) and all-cause mortality than their healthy counterparts. Specifically, they had a 45% increased risk of stroke, 26% increased risk of MI, 53% increased risk of heart failure, 26% increased risk of peripheral arterial disease, and 36% increased risk of all-cause mortality.[1]

The added risks were statistically significant despite adjustment for confounding factors such as age, gender, hypertension, diabetes, and other medical comorbidities, said coauthor Avnish Deobhakta, MD, at the New York Eye and Ear Infirmary of Mount Sinai in New York City.

Previous case series and longitudinal cohort studies that examined the association of RVO with stroke or MI produced inconsistent conclusions, Dr. Deobhakta said. He said he believes the current study settles the issue. "I think the evidence is pretty compelling that RVO is a sentinel event for cardiovascular risks," Dr. Deobhakta said. "I look at it now as a canary in the coal mine for these other systemic kinds of morbidity-inducing or even life-threatening health risks."

Hypertension in particular. Researchers in the United Kingdom and China assessed the impact of nine risk factors on the development of any type of RVO. Hypertension proved to be the strongest risk factor, followed by heart attack history, stroke history, and elevated levels of total cholesterol and creatinine.[2]

Overall, the researchers estimated, the global prevalence of any type of RVO was 0.77% in 2015, equivalent to 23.38 million cases of branch RVO and 6.7 million cases of CRVO. That was up from 16.4 million total cases worldwide of any type of RVO in 2008.

Urgent issue. Once RVO is diagnosed, Dr. Deobhakta suggested, the ophthalmologist should consider urgently referring the patient to a primary care physician for intensive medical management of the person's cardiovascular risks—and, possibly, should add a strong recom-

ated with a 42% increase of AAG, the researchers found. However, no association was found for current use of either gabapentin or pregabalin.

In addition, the incidence of AAG was associated with moderate drug exposure (3-5 prescriptions in the year before diagnosis). In contrast, neither limited exposure (1-2 prescriptions) nor significant exposure (6 or more) yielded an association with AAG. The small number of cases identified for significant exposure may have affected results, the researchers noted.

Method of action? The authors theorized that the mechanism of AAG associated with gabapentin use is similar to that of topiramate with regard to forward displacement of the ciliary body.

Clinical implications. While the findings need to be validated by other studies, Dr. Etminan suggested that ophthalmologists closely evaluate patients diagnosed with AAG who are on gabapentin. He added that it's possible that patients with a previous history of AAG might be able to safely take pregabalin instead. *—Miriam Karmel*

1 Browne MJ et al. *J Glaucoma*. 2019;28(9):777-779.
2 Goodman CW, Brett AS. *JAMA Intern Med*. 2019;179(5):695-701.
Relevant financial disclosures—Dr. Etminan: None.

mendation for prompt evaluation and follow-up by a cardiologist or neurologist.

"A retinal vein occlusion, by definition, is when a really small vessel in the eye is blocked or there's some kind of pathology with it. Well, if a really small vessel in the eye is showing that it can be affected in this way, then other vessels can have that kind of problem" as well, Dr. Deobhakta said. "And if we can prevent a stroke or other cardiovascular complication by sending these patients to the right specialists, or getting the right imaging tests, then that would be recommended." *—Linda Roach*

1 Wu CY et al. *Retina*. 2019;39(9):1635-1645.
2 Song P et al. *J Glob Health*. 2019;9(1):010427.
Relevant financial disclosures—Dr. Deobhakta: Alimera Sciences: C; Allergan: C.

PUBLIC HEALTH

Opioid Rx After Eye Surgery

HOW OFTEN DO PATIENTS WHO undergo incisional ocular surgery fill a prescription for an opioid medication? Despite increased awareness of the opioid crisis in the United States, researchers at the University of Pennsylvania found that the odds of having an opioid prescription filled after ocular surgery was more than 3 times higher in 2014-2016 than in 2000-2001.[1]

"Though opioid abuse has been declared a public health emergency, until now little has been known about the association between opioids and ocular surgery," said coauthor Brian L. VanderBeek, MD, MPH, MSCE, at the Scheie Eye Institute in Philadelphia. "The findings of our study provide a basis for discussing the role of opioids in post-ophthalmic surgical management."

Study specifics. The researchers used medical claims data from a U.S. insurer's database for the period of January 2000 through December 2016. For the primary analysis, the researchers looked at the rate of filled opioid prescriptions for each ophthalmic subspecialty surgery over time.

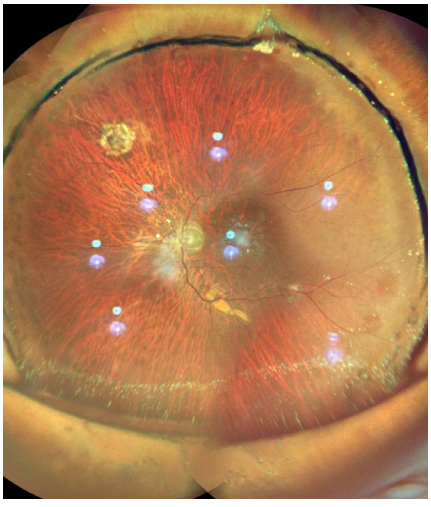
Results. A total of 2,407,962 incisional ocular surgeries were included; of these, 45,776 (1.90%) were associated with a filled opioid prescription. The lowest number of filled prescriptions was in 2000-2001, in which 671 prescriptions were filled for 53,912 surgeries (1.24%). In contrast, in 2016, 5,851 prescriptions were filled for 282,106 surgeries (2.07%). Multivariate logistic regression showed that year of surgery was significantly associated with filling an opioid prescription, with the highest odds in 2014 (odds ratio [OR] 3.71), 2015 (OR, 3.33), and 2016 (OR, 3.27).

The highest prescription fill rates were associated with strabismus surgery, trauma, and retina surgery.

Bottom line. These findings suggest the rate of filled prescriptions for opioid medications are increasing for all types of incisional ocular surgery over time, the researchers said. They concluded, "Given the ongoing national opioid epidemic, we hope the trends of increased prescription use we have described will motivate clinicians to evaluate their opioid prescribing practices to help in reversing the epidemic."

To help reduce unnecessary opioid prescribing, the CDC has published guidelines that cover such topics as risk assessment, drug selection, dosing regimens, and appropriate follow-up.[2] *—Arthur Stone*

1 Kolomeyer A et al. *JAMA Ophthmol*. Published online Sept. 19, 2019.
2 Dowell D et al. *MMWR Recomm Rep*. 2016;65(1):1-49.
Relevant financial disclosures—Dr. VanderBeek: NEI/NIH: S; Paul and Evanina MacKall Foundation: S; Research to Prevent Blindness: S.



TYPICAL RECIPIENT. *Scleral buckling surgery is one of the top three ocular surgeries for which patients are likely to be prescribed an opioid medication.*

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.

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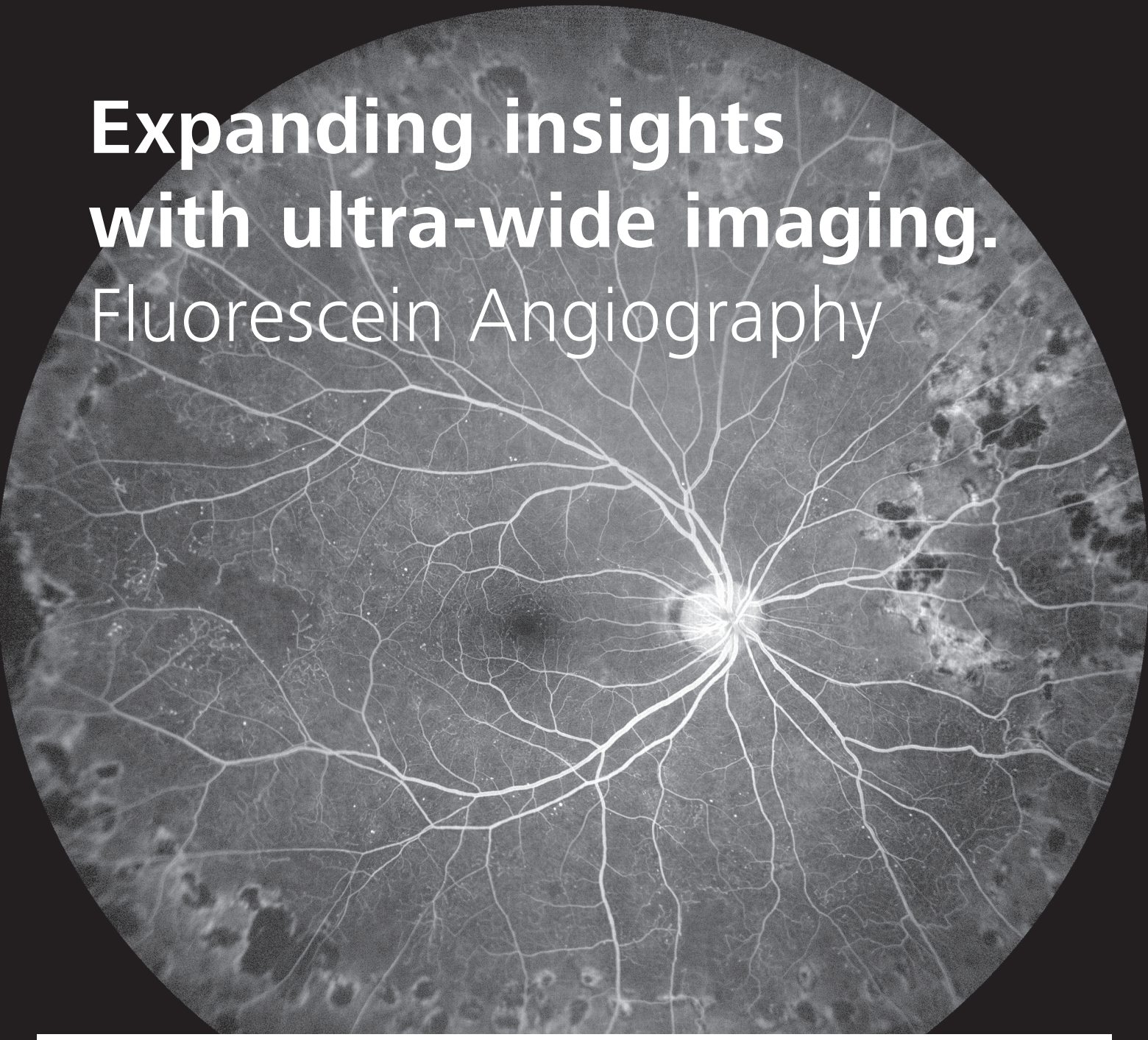

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Deep Learning for Identifying Eyes at Risk for Glaucomatous Optic Neuropathy

December 2019

Phene et al. developed an algorithm based on deep learning and tested its effectiveness for photographic features of the optic nerve head (OHN) that would prompt referral for further evaluation of glaucomatous optic neuropathy (referable GON). They found that a deep learning algorithm trained solely on fundus images has greater sensitivity than eye care providers for detecting referable GON; specificity was comparable for the two methods of detection.

The fundus images used in this research were obtained from screening programs, published studies, and a glaucoma clinic. The algorithm was trained using 86,618 images that also were graded by eye care providers for glaucomatous ONH features and referable GON. Of the 43 graders, 14 were fellowship-trained glaucoma specialists, 26 were comprehensive ophthalmologists, and three were optometrists.

The algorithm was validated using three datasets: 1) Dataset A included 1,205 images (one per patient; 18.1% referable) adjudicated by panels of glaucoma specialists; 2) dataset B consisted of 9,642 images (one per patient; 9.2% referable) from a diabetic teleretinal screening program; and 3) dataset C comprised 346 images (one per patient; 81.7% referable) from a glaucoma clinic. Outcome measures were area under the receiver operating characteristic curve (AUC), sensitivity, and specificity for referable GON and glaucomatous ONH features.

The algorithm's AUC for referable GON was 0.945 in dataset A (95% confidence interval [CI], 0.929-0.960), 0.855 in dataset B (95% CI, 0.841-0.870), and 0.881 in dataset C (95% CI, 0.838-0.918). AUCs for glaucomatous ONH features ranged from 0.661 to 0.973. The sensitivity of the algorithm was significantly higher than that of seven of 10 graders not involved in determining the reference standard, including two of three glaucoma specialists. The specificity of the algorithm exceeded that of three graders (including one glaucoma specialist) and was comparable to that of other graders. The algorithm performed favorably across independent datasets. According to specialists and the algorithm, crucial features of referable GON were vertical cup-to-disc ratio ≥0.7, notching of the neuroretinal rim, abnormality of the retinal nerve fiber layer, and baring of the circumlinear vessels.

The authors suggested that algorithms such as this one may improve the effectiveness of glaucoma screening in settings without clinicians who can interpret ONH features.

OCT Predictors of DR Progression and DME

December 2019

Sun et al. assessed the relationship between metrics of optical coherence tomography angiography (OCTA) and the progression of diabetic retinopathy (DR) and development of diabetic macular edema (DME) in patients with diabetes. They identified key predictors of DR progression and DME development, thus supporting the predictive value of OCTA.

This prospective study included 129 patients (205 eyes) with diabetes who were monitored for at least two years. OCTA images of the superficial and deep capillary plexuses were generated by digital software. After a quality check, automated measurements were obtained of the foveal avascular zone (FAZ) area, FAZ circularity, vessel density, and fractal dimension of the superficial and deep capillary plexuses. Main outcomes were progression of DR and development of DME.

During follow-up (median, 27.14 months), DR progressed in 28 (13.7%) of the 205 eyes. Of the 194 eyes without DME at baseline, 17 (8.8%) developed the condition during the study. After adjustment for established risk factors (DR severity, HbA_{1c} levels, age, diabe-

tes duration, and mean arterial blood pressure), significant predictors of DR progression were larger FAZ area, lower vessel density, and lower fractal dimension of the deep capillary plexus. With regard to DME development, lower vessel density of the superficial capillary plexus proved to be the significant prognostic factor.

In summary, better predictions of DR progression and DME can be attained by combining OCTA metrics with traditional risk factors, said the authors. Additional studies are needed to determine whether such metrics could identify subgroups of patients with DR who might benefit from more intensive workups or proactive treatment.

Imaging Nonperfusion in Patients With DME: Comparing Techniques

December 2019

Couturier et al. compared retinal nonperfusion observations for two imaging modalities after anti-VEGF treatment of diabetic macular edema (DME). They found that swept-source widefield optical coherence tomography angiography (SS-WF OCTA) performed better than ultra-widefield fluorescein angiography (UWF FA) in detecting nonperfusion. However, after three treatment sessions, neither modality demonstrated reperfusion of arterioles or venules in areas of nonperfusion, despite improvement in the severity of diabetic retinopathy (DR).

This study was performed in nine patients (10 eyes) who had proliferative or severe nonproliferative DR. All received three intravitreal anti-VEGF injections for their DME, and all eyes were imaged with UWF color fundus photographs, UWF FA, and SS-WF OCTA. Imaging took place at baseline and one month after the third injection. The images were aligned and then divided into 16 identical boxes for analysis by two masked retina specialists. Main outcome measures included discrepancies in detection of nonperfusion between the two imaging modalities; assessment of DR severity by UWF fundus photographs; and changes in each area of nonperfusion between baseline and follow-up. (For the latter, this included the number of 1) boxes per eye with at least one area of nonperfusion, 2) arterioles or venules that disappeared or reappeared, and 3) areas of nonperfusion in which capillaries disappeared or reappeared.)

Results showed that DR severity improved by at least one stage in eight of the 10 eyes. Evidence of this included a decrease in the mean number of microaneurysms and retinal hemorrhages on UWF photography at follow-up (40 ± 28 vs. 121 ± 57 at baseline; $p = .0020$) and by regression of fundus neovascularization if it had been present. All areas of nonperfusion identified by UWF FA also were observed with SS-WF OCTA, but the latter detected additional areas at baseline in 29% of boxes. Neither modality showed reperfusion of arterioles or venules at follow-up, even when a reduction in dark areas was apparent by UWF FA. Retinal capillaries were visible only with SS-WF OCTA.

The authors concluded that the unchanged number of areas of nonperfusion implies that neovascular complications may persist even if DR improves. Absence of reperfusion following anti-VEGF therapy highlights the risk of visual loss in patients who miss scheduled treatments.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MPH

RNFL Maps and Deep Learning

November/December 2019

Wang et al. used full retinal nerve fiber layer (RNFL) thickness maps from patients with glaucoma and healthy controls to evaluate the diagnostic accuracy of four different machine learning algorithms. They found that all four models achieved similarly high diagnostic accuracies.

For this case-control study, the researchers evaluated 69 patients (93 eyes) with glaucoma and 128 healthy controls (128 eyes) from the Los Angeles Latino Eye Study (LALES). There was no significant difference in age, sex, best-corrected visual acuity, or axial length between the two groups.

RNFL maps centered on the optic nerve head were supplied to two conventional machine learning algorithms and two convolutional neural nets, one of which was a custom-made deep learning network. AUC (area under the curve) values for the four models were greater than 0.90 (range, 0.91-0.92). In contrast, the AUC for mean circumpapillary RNFL thickness was 0.76 in the same patient population.

The findings support the importance of the spatial structure of RNFL thickness map data in diagnosing glaucoma, the researchers said. They cautioned that as the study participants were from the LALES, the results may not be applicable to other ethnic populations. *—Summary by Jean Shaw*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Treatment of Retinal Tears and ERM Formation

December 2019

Retinal tears can be treated with laser retinopexy or cryoretinopexy. Is one method more likely than the other to lead to formation of an epiretinal membrane (ERM)? **Blackorby et al.** set out to evaluate this issue and found no difference in the incidence, timing, or severity of ERM formation between the two treatments.

For this study, the researchers evaluated the charts of patients treated at a single surgical site over a 11-year period. Data were available on 2,257 eyes (2,257 patients). Of these, 1,655 were treated with laser retinopexy, and 602 were treated with cryoretinopexy.

All told, 74 patients (3.2%) experienced an ERM after treatment for a retinal tear. Of these, 26 had undergone cryoretinopexy, and 48 had been treated with laser retinopexy. The average time to ERM development was 11.5 months for those in the cryoretinopexy group and 12 months in those who had received laser retinopexy ($p = 0.878$). Seven ERMs required surgical treatment; of these, two were in the cryoretinopexy group.

Given the lack of a statistically sig-

nificant difference in the incidence of macular ERM formation between the two groups, the researchers recommend that the choice of treatment for retinal tears rest on such issues as media clarity, retinal tear position, and extent of pathologic features.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Predicting POAG Progression With Machine Learning

December 2019

Can data-trained machine learning be used to identify glaucoma cases at high risk of progression? In addressing this question, **Baxter et al.** used a discrete event captured in the electronic health record (EHR)—surgical intervention—as a marker for progressive disease in patients with primary open-angle glaucoma (POAG). They found that some details in the EHR may have predictive value even if eye-specific data are lacking; pertinent information included blood pressure findings and certain classes of medication.

The authors collected EHR data for 385 patients with POAG who were treated at the same academic institution. The data were integrated into three models: multivariable logistic regression, random forests, and artificial neural networks. Leave-one-out cross-validation was applied. The performance of each model was tested by calculating mean area under the receiver operating characteristic curve (AUC) as well as sensitivity, specificity, accuracy, and the Youden index.

The analysis showed that multivariable logistic regression was the most effective model for predicting progressive disease that would require surgery (AUC, 0.67). The other models were close behind (AUC, 0.65 for both). In the logistic regression model, higher mean systolic blood pressure was found to significantly increase the likelihood of glaucoma surgery (odds ratio [OR], 1.09; $p < .001$). Conversely, lower likelihood of surgery was linked to use of ophthalmic medications (OR, 0.28; $p < .001$), nonopioid analgesics (OR, 0.21; $p = .002$), antihyperlipidemic medications (OR, 0.39; $p = .004$), macrolide antibiotics (OR, 0.40; $p = .03$), and calcium blockers (OR, 0.43; $p = .03$). The authors acknowledged that the favorable findings for nonophthalmic drug classes may support the exploration of possible new therapeutic targets.

Accuracy was similar for the three models, ranging from 0.60 (artificial neural networks) to 0.62 (logistic regression and random forests). The best Youden index was achieved with logistic regression (0.26). The random forests model had the lowest sensitivity and the greatest specificity.

This type of machine learning provides additional groundwork for developing automated risk predictions from systemic EHR data, which could improve clinical decision-making, the researchers said.

Quality of Life and Noninfectious Uveitis

December 2019

Niemeyer et al. set out to determine the time trade-off (TTO) utility values associated with noninfectious uveitis. They found that noninfectious uveitis is linked to modestly reduced quality of life (QoL), which correlated with long-term use of oral corticosteroids and poor visual acuity (VA) in the worse eye.

For this study, the researchers enrolled 104 consecutively treated adults with noninfectious uveitis. TTO utility values were calculated from responses to an interviewer-guided survey on QoL. The researchers also collected information about general health, ocular symptoms, and religion. Medical records were reviewed to determine anatomic location of uveitis, disease activity, VA, and treatments provided. Multivariable regression analysis with backward selection was used to identify factors associated with TTO scores.

Findings showed a median TTO value of 0.975 for the study population (interquartile range [IQR], 0.8-1.0), which corresponded to trading 1.28 years (median) of remaining life for healthy eyes (IQR, 0-6.29). According to regression analysis, controlled for age and sex, lower TTO scores were linked to poorer VA in the worse eye, taking oral corticosteroids for more than six months, and current use of antidepressants ($p = .008$, $p = .006$, and $p = .008$, respectively). Patients who had been taking oral corticosteroids for more than six months, regardless of the dose, were 10.5 times more likely to trade 20% or more years of remaining life (TTO ≤ 0.8) than were those who did not take oral corticosteroids ($p = .002$). Patients who were legally blind in at least one eye had a median TTO score of 0.8 and were willing to trade a median of 4.3 years of remaining life.

Overall, 73% of patients were willing to trade time from their life for healthy eyes. The backward stepwise analysis showed that the greatest contributors to this willingness were college education (odds ratio [OR], 5.12; $p = .008$) and Catholic religion (OR, 0.27; $p = .03$).

To the authors' knowledge, this study is the first to investigate TTO utility values among patients with noninfectious uveitis. The results highlight the negative effect of long-term use of corticosteroids on QoL, regardless of dosage. The TTO tool had favorable test-retest reliability and thus may be useful to study QoL for patients with ocular disease, the authors concluded.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Sex and the Ophthalmic Literature

November 2019

Is there a gap with regard to the sex of authors of ophthalmic studies? **Kramer et al.** performed a bibliometric analysis of published ophthalmic literature to compare authorship by sex and gain understanding of women's and men's preponderance and position in article bylines. The results showed that women represented roughly 35% of authorships and were less likely than men to have key roles in the research. However, in recent years, the percentage of women whose names appear first or last in the byline has increased.

For this study, the researchers looked at more than 10 years' worth of original English-language articles published in ophthalmology journals that are indexed in the Web of Science. Data were acquired in August 2018. Given names were used to determine the sex of each author. Articles originating from China, South Korea, and Taiwan were excluded because of the high number of unisex names. A prestige index, reflecting byline position, was calculated.

Outcome measures included the proportion of female authorships, odds ratios of women being listed first and last in bylines, rates of citation, and transnational female representation within ophthalmic research.

Overall, 87,640 original articles were published among 248 ophthalmologic journals. Of the 344,433 authorships, 120,305 were by females (34.9%). Women represented 37.1% of first-listed authors, 36.7% of coauthors, and 27.1% of authors listed last. The female-to-male odds ratio was 1.12 for first authorships, 1.20 for coauthorships, and 0.63 for last authorships. The annual rate of increase in authorship by females was 1.6% overall, 1.6% for first authorship, 1.3% for coauthorship, and 2.5% for last authorship. Women were underrepresented in prestigious authorships (prestige index, −0.22). Articles with women in key authorship roles were cited slightly less frequently than those with men in key roles. On average, females were less prolific than males: 42.5% of female authors were responsible for the 34.9% of all authorships. No particular journal or country provided better chances for women to be in prestigious authorship roles.

The authors forecast that female authorship will grow to 44.1% by 2028, accompanied by sex-neutral distribution of prestigious roles. *(See also related commentary by Irena Tsui, MD, in the same issue.)*

Assessing Online Information on Diabetic Retinopathy

November 2019

Kloosterboer et al. took a close look at various websites that contain patient information on diabetic retinopathy (DR) and found that the content was generally poor in quality, difficult to interpret, and not suitable to help patients make sound medical decisions.

For their study, the authors developed a 26-item survey that addressed questions of relevance to patients and applied it to 11 websites with DR content to assess accuracy and completeness of freely available material. Included were news sites, WebMD, All About Vision, EyeWiki, Mayo Clinic, and national ophthalmic associations and societies. Readability was analyzed with an online tool, and each website was evaluated independently by a vitreoretinal surgeon and two vitreoretinal fellows. *JAMA* benchmarks were used to determine the quality of each site's content.

The mean (standard deviation [SD]) questionnaire score among the 11 sites was 55.76 (13.38) of 104 possible points. The quality of content varied among the sites ($H = 25.811$, $p = .004$). The mean (SD) reading grade for all websites was 11.30 (1.79), which equates to the 11th-grade reading level; however, 6th grade is the level recommended by the U.S. Department of Health and Human Services. WebMD was found to have the lowest degree of complexity. There was no correlation between content accuracy and the mean reading grade or the Google rank. No website achieved all four *JAMA* benchmarks, and only one site achieved three of the four. Four sites did not meet any *JAMA* benchmarks. No correlation was found between content accuracy and the number of *JAMA* benchmarks achieved. Reproducibility was similar among the three observers.

Given the uneven accuracy of online DR information, the authors emphasized the importance of directing patients to reliable sources. *(See also related commentary by Rahul N. Khurana, MD, in the same issue.)*

Anti-VEGF Comparison in RCT for CRVO-Related Macular Edema

November 2019

Hykin et al. compared the clinical effectiveness of ranibizumab, aflibercept, and bevacizumab for managing macular edema due to central retinal vein occlusion (CRVO) in a randomized clinical trial. They found that, at 100 weeks, aflibercept outcomes were noninferior (not worse) to ranibizumab outcomes; results for the comparison of bevacizumab versus ranibizumab were inconclusive, that is, they could not determine if the outcomes were worse or not worse with bevacizumab. In a post hoc analysis, they also noted the comparison of bevacizumab versus aflibercept were inconclusive.

The authors' main objective was to determine whether intravitreal administration of either aflibercept or bevacizumab, in comparison to ranibizumab, results in a noninferior mean change in vision at 100 weeks for eyes with CRVO-related macular edema. For this prospective study, they enrolled 463 adults treated at 44 ophthalmology departments of the U.K. National Health Service. The mean age of the study population was 69.1 years; 57.2% were male.

All participants had visual impairment of less than 12 months' duration caused by CRVO-related macular edema. Best-corrected visual acuity (BCVA) in the study eye ranged from approximately 20/32 to 20/400. Central subfield thickness according to spectral-domain optical coherence tomography was at least 320 μm in the study eye.

The patients were assigned randomly to receive repeated intravitreal injections of ranibizumab (0.5 mg/0.05 mL), aflibercept (2.0 mg/0.05 mL), or bevacizumab (1.25 mg/0.05 mL) during a 100-week period. The main outcome was the adjusted mean change in BCVA in the study eye at week 100. Noninferiority was concluded if the lower bounds of 95% confidence intervals (CI) for both the intent-to-treat and per-protocol analyses were above –5 letters.

At week 100, the mean (standard deviation) gain in BCVA letter score was 12.5 (21.1) for ranibizumab, 15.1 (18.7) for aflibercept, and 9.8 (21.4) for bevacizumab. Aflibercept was found to be noninferior to ranibizumab (intent-to-treat adjusted mean BCVA difference, 2.23 letters; 95% CI, –2.17 to 6.63

letters; p < .001). Bevacizumab was not found to be noninferior to ranibizumab (intent-to-treat adjusted mean BCVA difference, –1.73 letters; 95% CI, –6.12 to 2.67 letters; p = .07). In a post hoc analysis, bevacizumab also was not found to be noninferior to aflibercept (adjusted mean BCVA difference, –3.96 letters; 95% CI, –8.34 to 0.42; p = .32). Results of the per-protocol analysis were similar.

The mean number of injections was lower for the aflibercept group (10.0) than the ranibizumab group (11.8). There was a mean of 11.5 injections (95% CI, 10.7-12.4) in the bevacizumab group.

The authors cautioned that their results must be interpreted in the context of the eligibility criteria and treatment protocols used in this study.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Multimodal Imaging to Detect Melanoma-Prone Choroidal Nevi

British Journal of Ophthalmology
2019;103(10):1441-1447

With multimodal imaging, subtle details of choroidal nevi can be observed, potentially leading to earlier detection of incipient melanoma and better prognosis. **Dalvin et al.** used high-resolution ultrasonography, fundus autofluorescence (AF), and spectral-domain optical coherence tomography (OCT) to examine choroidal nevi. They found that certain combinations of previously identified risk factors signal a high risk of progression to melanoma.

This retrospective study included 3,806 choroidal nevi (in 3,584 eyes of 3,334 patients), diagnosed consecutively during a 10-year period. In a prior study, these cases were evaluated by clinical examination and multimodal imaging, and six risk factors for transformation to melanoma were identified:

- tumor thickness >2 mm on ultrasonography
- presence of subretinal fluid on OCT
- visual acuity loss to 20/50 or worse
- orange pigment by AF
- hollow acoustic density on ultrasonography
- largest basal tumor diameter >5 mm by photography

In this study, a total of 2,355 nevi (2,211 eyes; 2,075 patients) were monitored for an average of three years (range, <1-11 years). No nevus had all six risk factors. The five-year Kaplan-Meier estimated risk of a choroidal nevus transforming to melanoma was 1% with no risk factor (hazard ratio [HR], 0.1), 11% with one factor (range, 9-37%; HR, 2.1-7.8), 22% with two factors (range, 12%-68%; HR, 1.8-12.1), 34% with three factors (range, 21%-100%; HR, 4.0-24.4), and 55% with four or five factors (range, 0%-100%; HR, 4.6-170.0 and 12.0-595.0, respectively). The highest-risk combination of three factors included decreased visual acuity, orange pigment, and hollow acoustic density (HR, 29.0). Among nevi with four risk factors, the most concerning combination was tumor thickness >2 mm, subretinal fluid, visual acuity loss, and orange pigment (HR, 170). Risk factors responsible for the highest HR, in any set of two to five factors, were visual acuity loss and orange pigment.

The authors recommend multimodal imaging to guide choroidal nevi management. Detecting high-risk features may prompt referral to an ocular oncologist, whereas observation may be adequate for lower-risk nevi.

Methotrexate Versus Mycophenolate Mofetil for Uveitis

JAMA
2019;322(10):936-945

Corticosteroids are standard first-line treatment for noninfectious uveitis, but local and systemic side effects are common with these drugs. Alternatively, patients may receive antimetabolite treatment with methotrexate or mycophenolate mofetil, sparing them the adverse effects of steroids. In the FAST (First-line Antimetabolites as Steroid-sparing Treatment) trial, **Rathinam et al.** compared the efficacy of these two agents in patients with active noninfectious uveitis and found methotrexate to be noninferior to mycophenolate mofetil.

FAST was a randomized, parallel, observer-masked clinical trial conducted in six diverse countries. Patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis were assigned randomly to receive methotrexate (25 mg weekly) or mycophenolate mofetil (1.5 g twice daily); both agents were administered orally. Patients also were given oral prednisone, with the goal of tapering to 7.5 mg daily by six months. Topical corticosteroids were allowed if needed, and they were to be reduced to <2 drops/day of 1% prednisolone acetate.

The primary outcome, treatment success, was determined at months 6 and 12. Treatment success was defined as inflammation control, achievement of the target corticosteroid dosage, and acceptable safety and tolerability. Patients with treatment failure at month 6 received the other antimetabolite for the next six months.

Of the 216 patients enrolled, 194 had follow-up through six months, at which time the treatment success rate was 66.7% for methotrexate (64 of 96 patients) and 57.1% for mycophenolate mofetil (56 of 98 patients). Subgroup analysis of patients with posterior uveitis or panuveitis showed that methotrexate was more effective.

The 12-month evaluation was completed by 163 patients. About three-fourths of those with treatment success at six months continued to have control of inflammation at 12 months, and approximately half discontinued prednisone by this time. Among the 49 patients who switched treatment after the initial six months, those who transitioned to methotrexate had greater treatment success. Relatively few patients in either group had intolerability or safety issues, although liver function tests were more likely to be abnormal in those patients given methotrexate.

In summary, methotrexate was noninferior to mycophenolate mofetil as steroid-sparing immunosuppressive therapy for uveitis. Anatomic subtype may affect the success of either treatment; this possibility warrants further exploration, said the authors.

—Summaries by Lynda Seminara

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Who's on Call? Emergency Care Crisis Looms

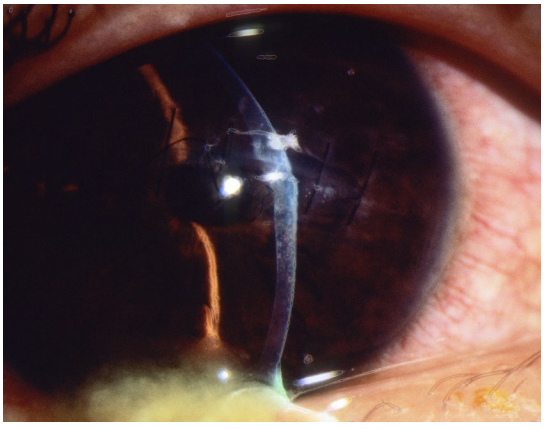
A dangerous trend has been percolating in emergency medicine over the past few decades. Across all specialties, fewer and fewer physicians are willing to provide on-call coverage at hospitals, both for the emergency department (ED) and for inpatient consultations. As more community hospitals face the difficulty of obtaining specialty coverage, the burden is falling on academic medical centers to care for a growing number of transferred patients.

What role does ophthalmology play in this growing crisis? "Without a doubt this problem is occurring across many specialties," said Charles F. Pattavina, MD, at St. Joseph Hospital in Bangor, Maine. "However, in my own experience—and I've heard this over and over—ophthalmology coverage does seem to be the biggest problem in most places."

What's Behind the Trend

Dr. Pattavina is well aware of the slow decrease in call coverage over the years, given his participation in the Maine Medical Association and the American College of Emergency Physicians. "This isn't a generational thing either," he said. "It's part of how ophthalmology has evolved as a profession. It's important to know why this is occurring and how all parties involved can help reverse the trend."

Growth of ASCs. "Simply put, we don't need to be affiliated with a hospital anymore in order to practice ophthalmology," said Robert A. Mazzoli, MD, FACS, a retired ophthalmologist in Steilacoom, Washington, who serves as the ophthalmic consultant to the American College of Surgeons' National Committee on Trauma. "The boom in ambulatory surgery centers [ASCs] has changed the game. We're in our own private practices. We all have our own ASCs or use somebody else's to perform most of our procedures. And so we no longer require hospital privileges to either perform surgery or build a successful practice via patient referrals. As a result, we're excused from any mandates and required participation in hospital call rosters."



TRAUMA. *When's the last time you repaired a corneal laceration? This patient's injury occurred during a game of basketball.*

Outdated ED equipment? Unease regarding surgical equipment is also an issue, said Dr. Mazzoli. "As ophthalmologists, we're chasing the most up-to-date technology." But because ophthalmology has shifted away from the hospital, "there is little motivation for the hospital to equip itself with what we would consider state-of-the-art equipment." Thus, he asked, even if the facility has "basic diagnostic and therapeutic ocular equipment, do I feel comfortable evaluating or repairing an open globe if there is no ultrasound in the ED, or the slit lamp is of poor quality and unserviced, or the microscope is 15, 20, or 30 years old? Does the OR have the right supplies, well-kept instruments, and experienced techs?"

Growth of specialization. Ophthalmology's focus on expertise is also stifling ED call, said Jeffrey D. Henderer, MD, at the Lewis Katz School of Medicine at Temple University in Philadelphia. "Many of us have specialized in one particular aspect of ophthalmology and have become very good at that [sub]specialty. But ED call is almost by definition going to be a jumble of injuries that fall outside many ophthalmologists' wheelhouse. For example, if an oculoplastic subspecialist is unfamiliar with globe trauma, repairing a ruptured globe might just be too far out of his or her comfort zone. By the

BY MICHAEL MOTT, CONTRIBUTING WRITER, INTERVIEWING **JEFFREY D. HENDERER, MD, ROBERT A. MAZZOLI, MD, FACS, CHARLES F. PATTAVINA, MD, CHRISTOPHER J. RAPUANO, MD,** AND **ROBERT E. WIGGINS JR., MD, MHA.**

same token, a cataract surgeon might feel ill-equipped to handle eyelid or tear duct trauma."

What's at Stake

A study by the CDC found that approximately 1 in 5 unanticipated events resulting in death or serious injury in hospital EDs could be attributed to the absence of specialty services.[1] "As doctors in general, it's our obligation to care for patients and try to prevent these types of occurrences," said Christopher J. Rapuano, MD, at Wills Eye Hospital in Philadelphia. "The public has an expectation that a certain level of quality care will be available to them any time of the day. It's our responsibility to provide ophthalmic specialty care 24/7. We all need to share in this duty. When only a few ophthalmologists take call, it's a huge burden on a relatively small number of physicians."

Optometry makes inroads. If ophthalmologists continue removing themselves from emergency medicine and remain unwilling to provide care outside of their offices, be warned, said Dr. Mazzoli: Doing so is only creating a void that others will be more than happy to fill. And they have made their intentions clear. Most recently, optometry has organized alongside the University of Massachusetts Medical School to push for an ED avoidance model in which certain patients would be diverted to the care of ODs in order to avoid stretching EDs' already strained resources.

"This is a serious situation," said Dr. Mazzoli. "Optometrists and nonophthalmic providers are organized and ready to jump in. They see the gap in care. If a hospital can't depend on ophthalmologists, why wouldn't they send patients elsewhere? Why wouldn't optometrists become the gatekeepers?"

As the American Optometric Association states, "The expanding scope of optometric practice, wide geographic distribution of optometrists, and force of health care reform have made the services of optometrists attractive to hospitals."[2] But as Dr. Pattavina pointed out, this is not the preference of hospital staff. "At St. Joseph, yes, we developed a workaround that involves ODs when MDs weren't available—but that's not what we want. Fortunately, a local ophthalmology group stepped up at the last minute, so we didn't have to resort to that plan."

Dr. Pattavina noted, "When we need help with an eye emergency, I can tell you with certainty that all of the emergency physicians want an ophthalmologist nearby rather than an optometrist." From a practical perspective, he added, "We rarely need the consultants to [physically] come in; the vast majority of our calls are for advice or follow-up."

Getting Back in the Game

Given the need for ophthalmology to reestablish its presence, what are some strategies to improve systems for emergency care and also reduce the ED call burden for everyone involved?

"There will be different solutions for different communities," said Robert E. Wiggins Jr., MD, MHA, at Asheville Eye Associates in Asheville, North Carolina. "There's really not a one-size-fits-all strategy. But any successful solution will begin and end with solid communication."

A regional approach. At a broad level, a capabilities-based assessment can be a very useful approach to identify the needs and gaps in the delivery of care, said Dr. Rapuano.

This approach involves getting all important community stakeholders together—ophthalmologists in private practice and in academia, emergency physicians, OR staff, hospital administrators—to see what's missing and what's causing the problem. Is it manpower? Are patients not being seen in the correct facility? Are they going to the ED when they should be coming into the ophthalmologist's office? Is specific equipment needed in the ED?

"This give-and-take approach is most effective when you have all of the numbers out in front of you," said Dr. Rapuano. "So, we've got X number of operating rooms, X number of ophthalmologists, X number of residents, and so on. Over the past X number of years, we've had X number of ophthalmic emergencies and X number of ruptured globes and corneal abrasions. How can we solve the equation in a way that is fair and kind for patients, hospitals, and doctors?"

Shared call pools. Another regional strategy might be the most obvious, said Dr. Henderer, and that's developing shared call pools among providers. "Plain and simple, we need to get more ophthalmologists in the pool—whether they are employed as part of a health system, in private practice, or residents," said Dr. Henderer. "The more ophthalmologists involved, the less the burden on each individual." For example, in northern Delaware, a group of about 18 ophthalmologists, many of whom are in their own separate private practices, cover call for each other on weekends. "They take call three to four weekends a year, and it's been successful," said Dr. Henderer.

Dedicated regional centers? Another option would be to establish regional centers that would be dedicated to the care of eye trauma. Under this model, ophthalmologists would share call at a single location where everything necessary to provide optimal care is available.

In addition to this central facility, Dr. Mazzoli said, "a regional system would identify facilities of varying capabilities that would be resources for both the EDs and responding ophthalmologists. In that way, a regionally designated facility could act as the initial advice center for the EDs, which could call that facility—similar to calling a regionally designated poison control center." Additionally, he said, "an ophthalmologist in a poorly served location could call the more sophisticated regional facility for specific advice as well as to establish early communications for transfer, if needed." This sets up a tiered system of capabilities that could be designated in a manner similar to the way the American College of Surgeons has designated Level 1 trauma centers, he said.

Telemedicine. Evaluating patients remotely offers another option for serving on call. "At Temple University, we have a HIPAA-compliant texting service (TigerConnect) through which we can take photographs and video of patients and share with residents, faculty, and ED staff," said Dr. Henderer.

The immediate transfer of knowledge is a major benefit. "For example, in a case of major trauma, an ED resident or physician sends me external photos and ultrasound video so I can quickly evaluate and relay what steps they have to perform right now and what can wait until an ophthalmologist arrives."

Military ophthalmology. Surgeons in the U.S. Armed Forces are interested in providing more trauma care during peacetime to increase their readiness for treating war-related injuries. Could this be a win-win solution for both community hospitals and military ophthalmologists? "It's certainly holds promise," said Dr. Mazzoli. "And it's a situation that currently only exists at the Brooke Army Medical Center in San Antonio, where military surgeons are providing care to the community at large. Can that model be expanded across the country? Yes, but it will take national legislation."

Negotiating ED Call

Traditionally, many ophthalmologists have provided uncompensated call coverage. But any time spent away from private practice to take ED call could have an impact on practice profitability, which is of concern in today's era of decreasing reimbursements and current economic pressures. As a result, an increasing number of ophthalmologists are negotiating with hospitals for emergency coverage compensation.

"Traditionally, most of us haven't been in a very good bargaining position with hospitals," said Dr. Wiggins. "They have the size, the resources, and the data. But that's no longer the case. The Academy is now providing members with access to the results of a recent survey assessing fair market value for call compensation across medicine. You can view what hospitals are currently paying ophthalmologists relative to other specialists as well as other important benchmarking data points to arm yourself with as you enter negotiations."[3]

But as Dr. Henderer pointed out, many hospitals have a fraught relationship with paying for call, so prepare yourself for an uphill battle. "They would rather not pay for what they are used to getting for free. But it's really a matter of letting the hospital know that your own practice requires revenue generation and that any time away from your practice isn't cost-effective unless you get reimbursed for it." Thus, you'll need to collect your own data. A good starting point for any negotiation is knowing what your fixed costs are and how much compensation you require to cover these costs if you're out of the office.

Additional factors. There are many other variables in addition to financial compensation to keep in mind when negotiating a contract for ED call, said Dr. Rapuano. "You'll need to know the hospital's medical staff guidelines to determine how often call may be required, how quickly you'll need to respond to a call, how many surgeries you will typically need to perform when on call, and whether or not you need additional malpractice coverage."

Perhaps most importantly, you'll also need to be familiar with the equipment and resources that will be available. "ED care is difficult enough given the late hours and urgent circumstances," said Dr. Rapuano, "so you'll want an operating room that you're comfortable with for delivering a certain quality of care." Will you have a vitrectomy machine, an indirect ophthalmoscope, a tonometer, or even a simple eye chart? Will you have dilating drops, sutures, and surgical drapes, or are these your own responsibility?

"It's also vital to know if the hospital will have a scrub nurse available who is acquainted with ophthalmology," Dr. Henderer added. "Being in an OR alongside someone who is unfamiliar with the anatomy of the eye or the necessary surgical instruments is a huge barrier to physician enthusiasm. In those circumstances, call can become somewhat of a DIY experience for the surgeon."

Healing a Rift

The withdrawal of ophthalmology from ED hospital call can have implications for your practice. It can affect recredentialing from certain third-party payers or can have a negative impact on referrals and patient volume.

"But let's not forget the potential damage on our professional reputation and our collegiality with other specialties," said Dr. Rapuano. "If we want to set ourselves up as being the experts in the eye, our response to our colleagues asking for help can't be 'not tonight' or 'I'm an expert in the eye but not that section of the eye.'" This disconnection from the hospital-based side of clinical care is precipitating the risk of other areas of medicine looking unfavorably at ophthalmology in general, added Dr. Mazzoli. "But we can repair that rift. If we can re-evaluate our responsibility in taking call, we can rejoin the house of medicine, so to speak. We can regain the support of our fellow surgeons as they rely on us to provide ophthalmic care to all patients in need."

1 Krueger KJ, Halperin EC. *Acad Med.* 2010; 85(12):1840-1844.
2 www.aoa.org/Documents/optometrists/facts-about-optometric-services-in-hospitals.pdf. Accessed Oct. 25, 2019.
3 *BFMV Physician Call Coverage Burden and Compensation 2019 Survey.* Available at aao.org/practice-management/analytics.

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Dr. Pattavina is an emergency physician at St. Joseph Hospital in Bangor, Maine. He is also past president of the Maine Medical Association and a former board member of the American College of Emergency Physicians. *Relevant financial disclosures: None.*
Dr. Rapuano is chief of the Cornea Service at Wills Eye Hospital in Philadelphia. *Relevant financial disclosures: None.*
Dr. Wiggins specializes in pediatric ophthalmology and neuro-ophthalmology and serves as the physician administrator for Asheville Eye Associates in Asheville, N.C. *Relevant financial disclosures: None.*
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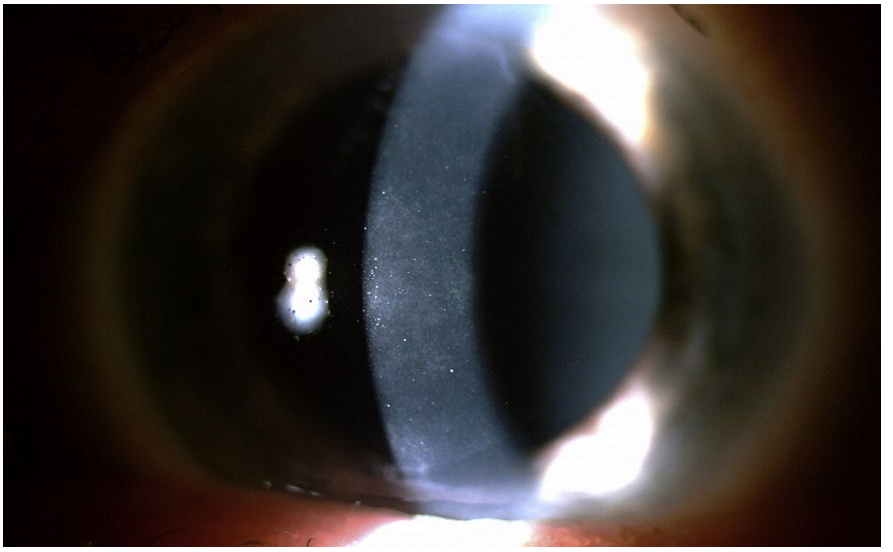
Wider Use of SMILE May Be on the Horizon

Over the last decade, SMILE has become the refractive surgery of choice for treating many myopes around the globe—except in the United States. That's because the FDA's initial indications for the only laser that can perform the procedure (VisuMax, Carl Zeiss) restricted U.S. surgeons to correcting cylinder of –0.50 D or less.

In October 2018, however, the FDA removed this roadblock. Now, U.S. refractive surgeons can use SMILE (which stands for small incision lenticule extraction) to correct myopia from –1.00 D to –10.00 D, with astigmatism of –0.75 to –3.00 D.

That makes SMILE "much more useful, because the majority of patients who present for refractive surgery have astigmatism as well as myopia. So, you can now treat 95% of refractive errors with SMILE," said Edward E. Manche, MD, at Stanford University in Palo Alto, California.



POST-OP ACUITY. *Visual acuity following SMILE typically recovers after the cornea has fully healed, as it did in this patient (note initial post-op haze).*

Impact: Cues From Asia

The impact that SMILE might eventually have on the U.S. refractive surgery landscape is best illustrated in China and other Asian countries, where myopia prevalence is high.

After a decade of VisuMax availability in China, more than 50% of the laser vision corrections there are SMILE procedures, and this number is likely to rise further, said John S.M. Chang, MD, at the Hong Kong Sanatorium & Hospital. "Researchers are now looking into customizing it, the way we do in LASIK with the excimer laser," Dr. Chang said.

Procedural Overview

With SMILE, the surgeon uses a femtosecond laser to incise a lenticule of intrastromal tissue 120 µm deep in the cornea. The lenticule is then separated from the adjacent stroma and removed manually through a 2- to 4-mm tunnel incision, which changes the cornea's shape and refractive power. Except for the small incision, the stromal fibrils and epithelium of the anterior corneal "cap" remain undisturbed, and Bowman's layer is preserved as a continuous layer.

The lenticule's thickness determines the amount of refractive correction from the procedure: approximately 13 to 14 µm per diopter, said Soosan Jacob, MS, FRCS, DNB, of Chennai, India. "Dissecting and removing the lenticules, some of which are quite thin, involves a learning curve. But [the procedure] is not difficult as long as you take the time to know what you're doing," she said.

Visual outcomes. With regard to early visual recovery, "You have a mild reduction in the 'wow' factor" with SMILE, Dr. Manche said. That's because final post-op acuity usually takes several days to develop with SMILE, in contrast to the typically good visual

BY LINDA ROACH, CONTRIBUTING WRITER, INTERVIEWING **JOHN S.M. CHANG, MD, SOOSAN JACOB, MS, FRCS, DNB, EDWARD E. MANCHE, MD,** AND **KEVIN M. MILLER, MD.**

Ivarsen A et al. *Ophthalmology.* 2014;121(4):822-828.

acuity (VA) on day one with LASIK.

Longer term, several meta-analyses have found no statistically significant differences between SMILE and LASIK when VA is measured after the cornea has healed, Dr. Chang said. These include mean uncorrected distance visual acuity (UDVA); percentage of eyes losing ≥1 lines of corrected distance VA (CDVA); mean post-op refractive spherical equivalent refractive error; and post-op refraction ±1 D of target, he said.

With regard to recent prospective studies, in a study of 70 patients, outcomes observed with SMILE were similar to those seen with LASIK at both the three- and 12-month marks.[1] In another study of 70 patients, visual outcomes and centration were comparable between the SMILE and LASIK eyes, although the functional optical zone was larger in SMILE eyes.[2]

Benefits

No LASIK flaps. SMILE eliminates flap-related complications like postoperative striae and late flap dislocations, and it results in fewer problems with dry eye in the early post-op period, Dr. Manche said. The procedure also is thought to have less of an impact on the cornea's biomechanical strength than LASIK does, to sever fewer corneal nerves, and perhaps to reduce the risk of ectasia, especially in higher myopes, he said.[3,4] However, these hypotheses have yet to be definitively confirmed.[5]

Better refractive predictability. SMILE also appears to offer better potential predictability of the post-op refraction, because corneal dehydration is not an issue, said Kevin M. Miller, MD, at the University of California, Los Angeles.

"When you do LASIK, as soon as you lift the flap the cornea beneath starts to dry out. The clock starts ticking, so you can get variable effects just from variable drying of the cornea. The drier the cornea gets for the exact same treatment, the greater the change is going to be in the cornea's refractive power, because every laser pulse evaporates more tissue when the tissue is dry," Dr. Miller said.

"This is actually a pretty huge issue, especially for the high corrections. When you're doing a very high LASIK correction, you're spending a lot of time with the flap off, and that drying effect can be very substantial on the final refractive outcome," he said. "But you don't have that with SMILE, because you're making the entire cut with the cornea unexposed to the air."

Greater patient acceptance. One of SMILE's strengths, in Dr. Chang's experience, is that it offers patients a better experience overall. To begin with, because there is no large corneal wound, patients do not have the foreign body sensation or excessive tearing that commonly occur in the first few hours after LASIK, nor do they experience persistent dry eye, he said.

The second advantage he sees is anecdotal: Patients have a lower "fear factor" with SMILE than with femtosecond LASIK, because of the time lag between the laser flap creation and the excimer laser ablation. With LASIK, he said, "after you do the first part—the femtosecond laser cut—you move them to the excimer, and by then the cavitation [bubbles] have gone away, so they can see your instruments moving and separating the tissue as you lift the flap. People just don't like having a doctor come at their eyes with sharp instruments. It makes them very scared."

But with SMILE, Dr. Chang said, "all those bubbles are still there, so they cannot see what you're doing as you come in with your surgical instruments and remove the lenticule. They aren't as frightened."

Challenges

Loss of suction. As with LASIK, and especially during a surgeon's earliest cases, there is a small risk that the laser's applanation cone will lose suction midway through a SMILE procedure, Dr. Jacob said. If this happens, there is a definite protocol to follow, and in most —but not all—cases, the surgeon can proceed with SMILE. Some cases might need to be converted to LASIK or PRK.

Zeiss is addressing this issue through training, Dr. Miller said. "The company, and I think wisely so, won't train you to be certified for SMILE until you've cut 50 flaps with the laser." (Of note, this will pose a challenge for surgeons who primarily do PRK and wish to convert to SMILE.)

Difficulties with lenticules. Low myopic SMILE corrections are the most challenging for the surgeon, because the lenticules are thin and fragile, and the surgeon must avoid tearing them and leaving torn tissue behind, Dr. Jacob said. "You just have to keep the proper techniques for handling the lenticules in mind."

Dr. Jacob added that surgeons "should make sure to dissect the anterior surface first, followed by the posterior surface. This prevents cap tears. And then you have to be sure to get the full lenticule out, or you can get irregular astigmatism." She has developed several surgical tips (see "More Online").

Need for retreatments. SMILE is so precise that enhancements are rarely required. For instance, Dr. Chang's unpublished analysis of his first 444 cases at his surgical center showed that 90.1% of eyes had UDVA of 20/20 or better, and 98.7% were at least 20/25.

However, if a patient is dissatisfied and wants an enhancement, many surgeons advocate doing this with PRK, Dr. Manche said. "I'm not keen on cutting a LASIK flap on top of the SMILE cap, because then you have multiple planes of incision on the cornea. So I typically perform PRK for SMILE enhancements." But some surgeons have reported successfully retreating undercorrected eyes by using SMILE plus LASIK, to correct as little as 0.5 D of refractive error, Dr. Chang said.

Fewer 20/20 outcomes? For now, as some research has demonstrated,[6] topographically guided LASIK may be more reliable than SMILE at giving more patients a VA of at least 20/20, Dr. Chang said. He also steers those patients who have a lot of higher-order aberrations preoperatively toward LASIK, "because we know how to correct those with LASIK."

Dr. Chang expects the VA gap to narrow when researchers develop customized SMILE algorithms. However, even if that does not happen, the small differences in VA will not dissuade an increasing number of his patients from choosing SMILE over LASIK, he said. "In my view 20/25 is still very good for

our patients, because in Hong Kong and China most people don't drive," he said. "When you don't drive, especially at night, 20/20 is not that important." As a result, he said, he is comfortable with recommending either procedure.

Financial barriers. The cost of acquiring a VisuMax femtosecond laser (more than $500,000) is the primary barrier that refractive surgeons face when considering SMILE. In most practices, this is passed on to patients as a premium price for the surgery.

But Drs. Manche and Miller said they want patients to choose their corneal refractive surgery based on weighing the pros and cons of each procedure, not on the price tag. Thus, the fee for laser vision correction at their centers is the same for PRK, LASIK, and SMILE.

The Road Ahead

Correcting hyperopia. So far, myopia and astigmatism are the only approved uses of the VisuMax laser for SMILE procedures. But a few groups are experimenting with correcting hyperopia by extracting stromal lenticules that have a central dimple, Dr. Chang said. For instance, earlier this year, Reinstein et al. published their three-month results from hyperopic SMILE in 82 eyes. For the 36 eyes targeted for emmetropia, UDVA was 20/40 or better in 89%.[7]

Transplanting the lenticules. Rather than tossing away the stromal tissue extracted during SMILE, Dr. Jacob and her colleagues have been exploring ways to transplant the lenticules onto damaged corneas, to jump-start healing of conditions such as corneal ulcers, she said. The lenticules also can be reshaped and implanted as corneal inlays for alleviating presbyopia.[8]

The Bottom Line

Any refractive surgery has pluses and minuses, but in the case of SMILE, the research supports giving it a place in refractive surgery.

"I tell patients that the visual acuity with SMILE is not quite as good as after custom LASIK, so if you really want the best possible VA results, then you should have LASIK. But I add that SMILE gives you fewer dry eye problems and is more comfortable," Dr. Chang said.

Overall, Dr. Manche said, "I think SMILE is an incredibly safe procedure. I don't think there are any glaring deficiencies with this technology. There are a few caveats to note. But there's no deal stopper in any of this."

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See the disclosure key, page 8. **For full disclosures,** view this article at aao.org/eyenet.

EXTRA **MORE ONLINE.** Dr. Jacob has developed a series of YouTube videos about SMILE; two are available at www.youtube.com/watch?v=xSq0jEYW8GM and www.youtube.com/watch?v=K4fMhvHyi7o.

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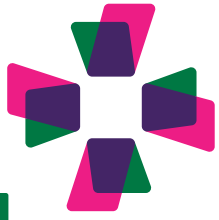

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Retinal Implants for RP: An Update on Argus II and Others

One in 3,500 people in the United States and Europe is affected by retinitis pigmentosa (RP), which predominantly affects retinal photoreceptor cells; secondary retinal neurons are relatively spared. Most RP patients will progress to near-total blindness. Several groups have developed variations of retinal prostheses for epiretinal or subretinal placement. These prostheses can help replace the function of the photoreceptors and stimulate secondary retinal neurons to create a visual image.

The Argus II device (Second Sight Medical Products) is the only FDA-approved epiretinal implant at this time. In 2002, Argus I, the first iteration of the device, which had 16 microelectrodes, was tested on human subjects who were enrolled in a phase 1 clinical trial. In 2011, Argus II, the second-generation device, with 60 microelectrodes, was approved for use in Europe. In 2013, after being granted Humanitarian Device Exemption status based on the safety and visual function results in 30 patients, it was granted U.S. FDA approval.

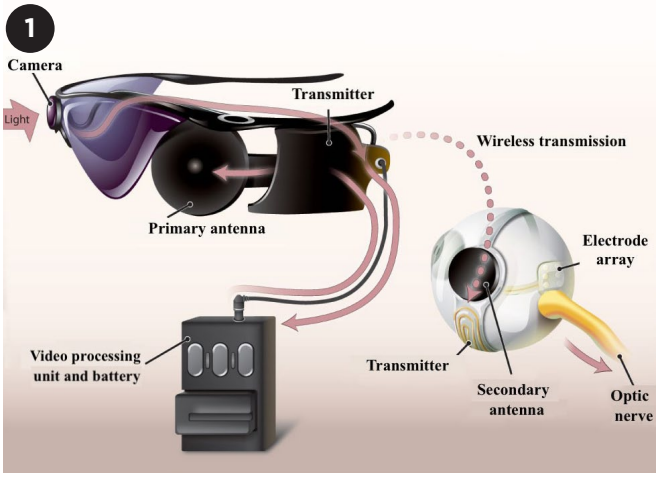
To date, more than 350 patients worldwide have been implanted with the Argus II retinal prosthesis.

Device Mechanism

The Argus II system has three main components: a video camera attached to the frame of the patient's glasses, a video processing unit (VPU) worn on a belt at the waist, and an epiretinal microelectrode-array implant connected to a secondary antenna (Fig. 1).

In real time, the VPU receives, processes, and converts the visual signal captured by the video camera into a brightness map. Data and power are wirelessly transmitted from the primary antenna, which is attached to the glasses, to the secondary antenna, which is sutured to the sclera in the lower temporal quadrant.[1]

The electronic data from the secondary antenna are then sent to the microelectrode array, which is implanted on the patient's retina. The array presents the brightness values from the video as pulse amplitudes on each of the 60 electrodes. This discrete signal is transmitted to the functioning secondary neurons, which help create a visual perception by processing and channeling the signal to the brain for final integration.



ARGUS II. *Components of the system.*

Indications

Based on the inclusion criteria of a five-year clinical trial reported by da Cruz et al., the Argus II system is indicated for individuals with end-stage RP who are 25 years or older, with slight or no light perception bilaterally (>2.9 logMAR).[1] The patient must have had functional form vision in the past to ensure intact optic nerve function and cortical processing. The worse-seeing eye is implanted with the Argus II prosthesis—and as the crystalline lens is removed during Argus II implantation, the patient can be pseudophakic or aphakic.

Patients' willingness and ability to adhere to long-term low-vision rehabilitation, device training, and clinical follow-up after Argus II implantation are important factors to consider when assessing candidacy. Anatomic features that may prevent successful implantation, such as posterior staphyloma or

BY **ROHAN BAJAJ, BS, GISLIN DAGNELIE, PHD, JAMES T. HANDA, MD,** AND **ADRIENNE W. SCOTT, MD.** EDITED BY INGRID U. SCOTT, MD, MPH, AND BENNIE H. JENG, MD.

Modified from Zrenner E. Sci Transl Med. 2013;5(210).

axial length above or below the 20.5 mm to 26 mm range, and conditions that may hinder the device's mechanism, such as impaired optic nerve function, exclude a patient from receiving the Argus II system.[1]

Surgical Technique

The surgical procedure for implanting the Argus II device is now well standardized. The sealed electronics enclosure and secondary antenna are attached to a silicone band that is placed around the globe and sutured onto the sclera like a scleral buckle. A vitrectomy is completed before introducing the microelectrode array into the eye through a pars plana sclerotomy. Finally, the microelectrode array is tacked to the retina over the macula.[1,2]

Benefits

It is challenging to test the effectiveness of the Argus II system because the patients who receive the device have little or no vision before implantation; therefore, common assessments such as visual field, visual acuity, and contrast sensitivity cannot fully quantify the real functional improvements in vision. It is important to note that it can take months for improvements to become apparent and stabilize because attaining adaptation to this new kind of vision requires a protracted learning process.

Instead, efficacy testing relies on assessing improvements in various aspects of daily living. Specifically, performance can be measured by tasks involving mobility and object discrimination and by questionnaires evaluating the patient's opinion about the device's effectiveness.

da Cruz et al. showed that, compared to the use of only residual vision, patients with the Argus II system activated were better at determining the direction of a moving object, performed better on an acuity task, and were more likely to locate a light shape on a dark background.[1] Additional studies have demonstrated a clear improvement in the visual function of patients when using the device. Some patients with baseline minimal light perception were able to perceive hand motions and count fingers after activation of the device.[3] Furthermore, those who most benefited were patients whose visual impairments were hindering their quality of life; after being implanted with the Argus II device, they reported considerable and sustained improvement in their quality of life.[4]

Long-Term Outcomes

No eyes were lost, and no patient's residual vision was damaged in the five-year clinical trial.[1] However, two of the 30 Argus II implants failed approximately four years after implantation due to a breakdown in the telemetry link between the primary and secondary antennae. The malfunction was thought to be caused by progressive exposure of the secondary antenna as a result of conjunctival erosion. In order to avoid this problem, Second Sight has modified the surgical procedure to cover the electronics case and sclerotomy site with processed human pericardium.[2]

In a separate study comparing the pre- and postoperative ocular coherence tomography images of 20 eyes, 50% were found to have developed a fibrosis-like tissue between the electrode array and surface of the retina.[5] In the majority of patients, the fibrosis advanced to retinoschisis; however, no change was noted in visual function.

Based on current and previously published studies, the Argus II system appears to be relatively safe, with a safety profile comparable to other ocular implants such as glaucoma drainage devices. Three postapproval studies sponsored by Second Sight in the United States (NCT01860092), France (NCT02303288), and Germany/Italy (NCT01490827) continue to monitor long-term outcomes.

Cost

Device pricing in countries where Argus II is approved has ranged from $115,000 to $150,000 (U.S. dollars). The price of the device does not include the cost of medical and surgical interventions, training, or lengthy visual rehabilitation. However, despite the high initial outlay, a study evaluating the cost of the Argus II device demonstrated that it was a cost-effective intervention when compared to the standard care for RP.[6] In the United States, Medicare carriers and most commercial payers have agreed to cover the cost of the Argus II for patients who are blind from end-stage RP, including evaluation, surgery, and rehabilitation.

Alternatives

In Europe, the IRIS II (Pixium Vision) and Retina Implant Alpha II AMS (Retina Implant AG), as well as the Argus II, are approved for use.

Like the Argus II, the IRIS II uses a VPU. However, the subretinally placed Alpha AMS uses a photodiode array that can simultaneously detect light and transfer a charge to the inner retina. Because of its subretinal placement, power supply with subdermal wires, and occipital connector, surgery is more technically challenging and takes longer for the Alpha AMS than for the Argus II.[7] Initial results have shown that the Alpha II AMS implant is able to provide functional improvements such as identifying household objects and outdoor orientation in patients with RP who have residual inner retinal function.[8] To facilitate direct comparison among various retinal implants, standardized assessment practices tailored to individuals with very low vision are needed.

Future Improvements

In its current form, the Argus II system can be improved by utilizing the modularity of its camera unit—camera modules with thermal sensitivity, depth selection, and zoom function are being used for specific environments, and they may soon be available to current Argus II implantees. Increasing the density and number of microelectrodes could also improve the functioning of the device because vision restoration is theoretically correlated with the number of microelectrodes.[9]

Alternatively, the diseased eye could be bypassed entirely with implantation of a prosthesis in the visual cortex. Second Sight announced in May 2019 that it plans to accelerate development and commercialization of its Orion Visual Cortical Prosthesis System, a brain implant, while temporarily suspending

production of the Argus II system.

Research and development of new devices capable of providing increased spatial resolution would allow for further improvements in real-world functional capacity and quality of life.

Conclusion

Retinal prosthetic devices offer hope to patients with RP by bypassing the function of lost photoreceptors. Although the Argus II system's safety profile has been validated through long-term clinical trials, ophthalmologists must select the appropriate patients; in addition, patients considering implantation must fully understand that the Argus II system provides limited visual restoration. Before proceeding, both patients and their ophthalmologists must set realistic expectations for improvement in daily activities and understand the long-term commitment required for functional rehabilitation.

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A Puzzling Pediatric Tumor

Eight-year-old Emily* had had numerous appointments with her optometrist for accommodative esotropia with 20/20 vision. This time, her mother brought her in for right eye pain described as a foreign body sensation. Emily incidentally mentioned to the optometrist that, for the last few weeks, she could no longer see her alarm clock with her left eye.

The optometrist found that her right eye had 20/20 visual acuity (VA) and mild corneal staining consistent with a small corneal epithelial defect. However, the VA in her left eye had declined to 20/40, and confrontation testing demonstrated a nasal visual field loss in that eye. Dilation revealed a large bulbous white lesion protruding from the temporal retina of the left eye. The optometrist had seen Emily four months earlier and was puzzled—and very worried—about this new, large growth. Emily was immediately transferred to the closest pediatric hospital.

We Get a Look

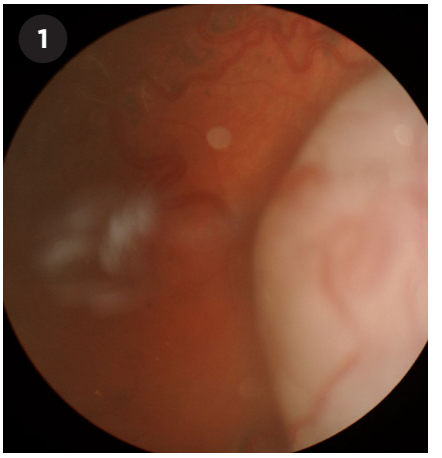
We examined her that same day. For an 8-year-old, Emily allowed us to perform a very thorough examination, though she would not let us do tonometry. Initial VA was 20/20 in her right eye and 20/200 in her left. Pinhole and manifest refraction did not improve her vision, and she had a left afferent pupillary defect. Eye movements were full. The anterior segment exam was normal in both eyes. The lens was clear, as was the vitreous in both eyes.

Examination of the fundus was normal in the right eye. In the left eye, the retina in the posterior pole appeared to be elevated with subtle subretinal fluid throughout the macula, with the elevation extending temporally and inferiorly to the location of the tumor. There were also areas of subretinal pigment clumps. A midtemporal area of retina was more elevated and appeared detached; anterior to this was a huge, whitish temporal mass extending into the vitreous, with engorged and tortuous feeder blood vessels (Fig. 1). A number of hyperreflective lesions were visible in the retina (Fig. 2). Optical coherence tomography confirmed the macular detachment.

She was immediately admitted to the hospital. Magnetic resonance imaging (MRI) and computed tomography (CT) both showed a temporal mass on the left eye with fluid under the retina extending posteriorly from the lesion (Fig. 3). No calcification was noted on these scans.

Next Steps

Retinoblastoma is always a consideration in a new tumor in a child. However, Emily's case was atypical for retinoblastoma, as she was older than the usual age of presentation, and no calcification was present. Over 80% of retinoblastomas have calcification, and 80% are diagnosed prior to age 4.



MYSTERIOUS MASS. *Large temporal tumor in the patient's left eye.*

Because of the serious retinal issue and the diagnostic uncertainty, she was sent to the nearest academic medical center to see a retina specialist for further evaluation. Fluorescein angiography (FA) was performed; no autofluorescence was seen, and there was early staining of the lesion and leakage in the late phases. This was not typical of Coats disease, one of the more common masquerade conditions for retinoblastoma. B-scan ultrasonography showed a tumor with surrounding retinal detachment and no calcification. The tumor measured 16 mm at its base and 5.6 mm in thickness.

The ambiguities introduced by the lack of calcification and Emily's age prompted referral that same day to a pediatric retinal physician, who confirmed that the tumor was retinoblastoma. Emily was then referred to an ocular oncologist for treatment.

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EDITED BY STEVEN J. GEDDE, MD.

Steve Gerber, MD

Differential Diagnosis

Several other retinal disorders have clinical features similar to those of retinoblastoma, leading to possible misdiagnosis. In children older than 5 years of age, the differential diagnosis includes Coats disease, toxocariasis, and familial exudative vitreoretinopathy (FEVR).

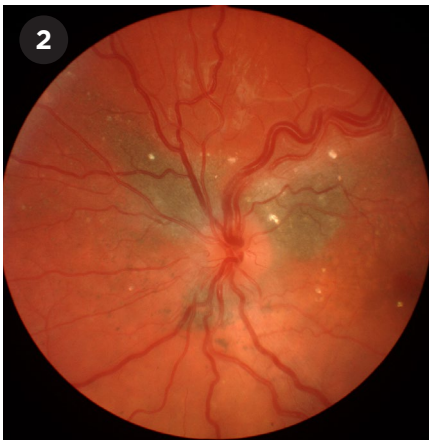
Coats disease. Coats disease remains one of the most difficult conditions to differentiate from retinoblastoma—and also one of the most misdiagnosed. Although Coats disease is more typically seen in patients older than those with retinoblastoma, the age ranges can overlap.

In this case, the primary differentiating factor between Coats disease and retinoblastoma was the presence of a solid mass in the retina on CT. In contrast with retinoblastoma, Coats disease causes a yellow, lipid-laden mass rather than a white lesion, and there is associated telangiectatic neovascularization.[1]

FA can be helpful, as the leakage in retinoblastoma occurs on multiple levels. In Coats disease, there are focal telangiectasias of small- to medium-sized vessels, with "light bulb" aneurysms and profuse subretinal leakage. Although the presence of calcium often helps to identify retinoblastoma, this finding is not universal, as demonstrated in Emily's case.

Toxocariasis. Ocular toxocariasis results from infection with the parasite *Toxocara canis* and can also present with a mass in the eye similar to retinoblastoma.[2] Even though ocular toxocariasis presents with a unilateral mass without calcifications, it is also characterized by subretinal granuloma formation or inflammation, especially in the vitreous, which did not occur in our patient.[2]

FEVR. The retinal findings in FEVR can be similar to those noted in Coats disease, with massive subretinal exudation. In addition, there may be avascular areas of peripheral retina and radial retinal folds. FEVR is a form of hereditary retinal dysplasia, inherited in an autosomal dominant pattern. Thus, there is often a known family history of the disease.



FUNDUS FINDINGS. *Posterior pole showing focal hyperreflective retinal deposits, subretinal pigment, and tortuous, dilated retinal veins.*

Discussion

Retinoblastoma is the most common form of childhood eye cancer, generally found in children younger than 5 years old. Emily's case is unusual because approximately 80% of retinoblastoma cases are diagnosed before the age of 4 years, with a median age at diagnosis of 2 years.[3] There are some reports of adults being diagnosed with retinoblastoma, but this is extremely rare.

Pathogenesis. Retinoblastoma has been characterized on a genetic level. The gene responsible, Retinoblastoma 1 (*RB1*), is a tumor suppressor gene.[3] A mutation of the gene leads to uncontrolled cell growth and creates the tumor seen in patients with retinoblastoma. While inherited mutations of *RB1* have been described, it is also possible for this mutation to happen sporadically. A "two-hit" hypothesis was described stating that after two different mutations occurred in that gene, a tumor would begin to grow.[3] In children with a family history of retinoblastoma, it is often the case that one hit was already inherited, making them prone to developing a tumor. However, it is still possible to obtain those two mutations sporadically.

The disease is unilateral in approximately two-thirds of patients and bilateral in one-third. Patients diagnosed with retinoblastoma are classified by whether the mutation is germline (present in all cells of the body) or somatic (present in the tumor only).

The germline mutation is what leads to an inheritable form of the disease, whereas the somatic mutation would only exist in that person.[3] Laterality can predict whether the retinoblastoma is caused by a germline or somatic mutation; bilateral tumors most often indicate a germline mutation. Although it was not confirmed whether Emily's tumor was caused by a germline or somatic mutation, based on presentation it can be assumed that it was mostly likely somatic.

Staging. Currently, the most commonly used method for staging retinoblastoma is the International Classification for Intraocular Retinoblastoma, which grades the tumor in order of increasing severity from A to E. This system is based on tumor size and location and whether vitreous or subretinal seeding is present. Emily's tumor was considered to be Group D because there was diffuse subretinal seeding more than 3 mm from the tumor and extensive subretinal fluid.

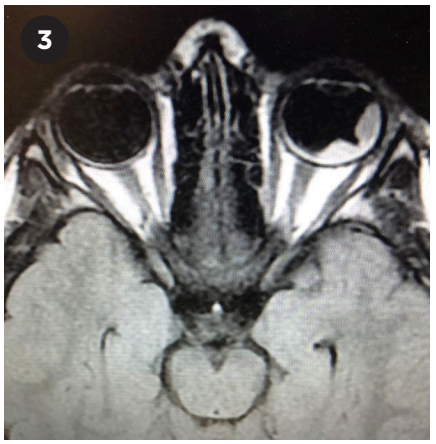
Treatment

The treatment plan for a retinoblastoma differs depending on whether the tumor is diagnosed as intraocular or extraocular. Intraocular tumors that are not metastatic can be treated locally, while metastatic intra- or extraocular tumors extending beyond the wall of the eye require either radiation or chemotherapy. Patients with smaller tumors can be treated with cryotherapy or laser therapy. Enucleation can also be part of management depending on vision and treatment potential. Emily's tumor was diagnosed as intraocular, based on the MRI.

Systemic chemotherapy. The drugs usually administered for retinoblastoma are vincristine, carboplatin, and etoposide, which can be given separately or in combination. Although chemotherapy is an effective means of reducing tumor growth, it carries the risk of multiple systemic adverse effects.

Radiation. Radiation therapy is a broad category that includes many different types of treatment options. Radioactive plaque treatment is used for focal tumors not in the macula.

Steve Gerber, MD



CLUES FROM MRI. *MRI shows the darkened temporal tumor mass, along with the lighter subretinal fluid.*

The benefits of this approach are that it helps preserve the patient's vision and diminishes radiation exposure to other parts of the body. Adverse effects of radiation therapy include damage to other parts of the eye that may lead to glaucoma, retinal detachment, bleeding, and second tumors later in life.

Intra-arterial chemotherapy. Previously, in advanced cases such as Emily's, the eye was enucleated because there was little hope of salvaging vision. However, intra-arterial chemotherapy (IAC) has revolutionized treatment by saving eyes that would otherwise have been enucleated while also sparing—or at least decreasing—the amount of chemotherapy and radiation needed.[4] Melphalan is the agent most commonly injected directly into the ophthalmic artery, resulting in tightly focused delivery of chemotherapy to the tumor.

Multiple studies have shown that IAC is effective as a primary treatment. In particular, it is used in advanced tumors. In a 2012 study, the effectiveness of IAC treatment was evaluated in 76 eyes of 67 patients with retinoblastoma. In treatment-naive eyes, the two-year probability of ocular salvage was 83% for eyes with subretinal seeding only, 64% for eyes with vitreous seeding only, and 80% for eyes with both.[5]

Among eyes that had previously been treated but had progressed, the two-year probability of ocular salvage was 50% for eyes with subretinal seeding only, 76% for eyes with vitreous seeding only, and 54% for eyes with both. The study concluded that, unlike radiation or systemic chemotherapy, IAC can usually obviate the need for enucleation.[5]

Adverse effects of IAC include eyelid edema, vitreous hemorrhage, hyperemia of the forehead, and temporary loss of the eyelashes. Complications include retinal artery occlusion, enophthalmos, choroidal occlusion, neovascular glaucoma, and direct toxicity to the retina.

Our Patient's Course

Emily had three treatments with IAC, which initially resulted in complete resolution of the tumor elevation and the subretinal fluid. Unfortunately, submacular fibrosis limited her final VA to 20/200. On a subsequent follow-up, she had new evidence of retinal seeding and received two additional IAC treatments at a higher dose. This treatment was selected to avoid radiation, large doses of chemotherapy, and enucleation. Recurrence of retinal seeding after these two additional IAC treatments led to the decision to enucleate the eye.

*Patient name is fictitious.

1 Ghorbanian S et al. *Ophthalmologica.* 2012; 227(4):175-182.
2 Fan CK et al. *Clin Microbiol Rev.* 2015;28(3): 663-686.
3 Corrêa ZM, Berry JL. Review of retinoblastoma. April 28, 2016. aao.org/disease-review/review-of-retinoblastoma. Accessed Sept. 27, 2019.
4 Zanaty M et al. *Scientific World Journal.* 2014; 2014:869604.
5 Abramson DH et al. *Br J Ophthalmol.* 2012;96 (4):499-502.

Mr. Kalafatis is a third-year medical student at the Indiana University School of Medicine in Indianapolis, **Ms. Myers** is a senior undergraduate at St. Mary's College in South Bend, Ind., and **Dr. Gerber** is in practice at Advanced Ophthalmology and is clinical professor of ophthalmology at the Indiana University School of Medicine in South Bend. *Financial disclosures: None.*

Deluged by Data

The Struggle to Close the Evidence-to-Practice Gap

Knowing is not enough; we must apply.
Willing is not enough; we must do.
—Goethe

By Annie Stuart, Contributing Writer

At the turn of the century, the Institute of Medicine published *To Err Is Human*[1] and *Crossing the Quality Chasm.*[2] "Both caught the attention of the public and policy makers," said Richard L. Abbott, MD, professor emeritus at the University of California, San Francisco. Although the first report focused on medical errors and the second on health care delivery issues, they also dovetailed with an already established and growing interest in evidence-based medicine.

For instance, in the late 1980s, the Academy introduced its clinical practice guidelines. Two issues that concerned physicians at the time were significant gaps in evidence and variations in practice among specialists including cardiologists, ophthalmologists, and orthopedists. "People became really interested in focusing on evidence, rather than just on professionals' prior experience or on expert opinion, often referred to as eminence-based medicine," Dr. Abbott said.

Since then, evidence-based medicine (EBM) has become an integral part of patient care. But keeping up with and implementing the latest evidence poses myriad challenges for physicians (see "Barriers to Quick Adoption," below). In fact, *Crossing the Quality Chasm* reported that the time between significant discovery and adoption into routine patient care averaged 17 years.[2] Although a lag between discovery and implementation is inevitable, it's important to look at EBM and how physicians, trial investigators, and organizations can work together to speed EBM to the clinic to ensure that patients receive the best current care.

The Evolving Role of EBM

Keys to effective practice include understanding EBM and knowing how to apply it to patients.

Evolution of EBM. Initially, EBM was defined as an approach to patient care in which decisions were based on clinical studies, ideally unbiased and well-designed randomized controlled trials (RCTs), said Dr. Abbott. The goals of EBM were to improve the patient's quality of care and outcomes and to minimize mistakes—and they still are, he said.

Today, however, a working definition of EBM has been expanded to include integration of the best available evidence with clinical expertise as well as the patient's preferences, values, and unique set of circumstances.[3,4]

EBM and your patients. This redefinition is much more than an academic exercise. "Clini-

Danny Schlitz

cal evidence is based largely on populations of patients, and those patients may differ a little or a lot from the patient sitting in front of you," said Jennifer K. Sun, MD, MPH. She is chair of the DRCR Retina Network (DRCR.net), a consortium of sites funded by the NIH to research diabetic eye disease and other retinal diseases. Patients in clinical practice, for example, may be much less compliant with follow-up visits or treatment than those intentionally recruited for and guided through clinical studies.[5]

"In addition, study outcomes often refer to average results across the entire group, which may not represent what will happen in an individual patient," said Dr. Sun. She gave the example of anti-VEGF studies conducted by the DRCR.net. "In many of our studies for diabetic macular edema [DME], patients on average did extraordinarily well, gaining 2 to 4 lines of vision, depending upon the type of agent used." However, some patients gained even more than the average, while others gained less or even, rarely, experienced vision worsening, she said.

This may be why some EBM experts consider an N-of-1 trial—how a particular patient responds—to be the highest level of evidence, even higher than that of an RCT, said Paul P. Lee, MD, JD, at the W.K. Kellogg Eye Center in Ann Arbor, Michigan. "Our vocation is to know about the findings and limitations of the RCTs so we have informed judgment about how we care for each patient."

Barriers to Quick Adoption

Although EBM has been part of the medical landscape for at least two decades, many barriers to quick adoption remain.

Physician perspective. "The biggest barrier is that physicians are extremely busy," said Dr. Abbott.

Time crunches. The stresses on physicians include not just patient care but also third-party demands such as documentation, negotiations with insurance companies, and other regulatory burdens, added Rahul N. Khurana, MD, at Northern California Retina Vitreous Associates in Mountain View, California.

"To adopt a new practice," said Dr. Abbott, "physicians may have to take courses and learn something new, whether gaining experience with a new drug or device." Adding to these time pressures is the huge volume of information available through the internet, peer-reviewed journals, meetings, and more, to which physicians may devote significant time in order to keep current. In fact, the amount of medical knowledge is estimated to double every two to three months.[6]

Choice Architecture

"Most people assume that education alone will lead to changes in medical decision-making. However, the design of our environment and the way information is framed has a significant impact on how we behave," said Mitesh Patel, MD, MBA, at the Penn Medicine Nudge Unit, which uses behavioral economics and psychology to influence medical decision-making.

Choice challenges. Using technology to encourage behavioral changes, both in patients and clinicians, can be extremely useful, agreed Dr. Kerr, but physicians sometimes view this as an abdication of autonomy.

"EHR notifications have also become a little bit of a tragedy of the commons," added Dr. Scherer. "Everybody has a great idea for an intervention to nudge clinicians to remember something or do something slightly different. When they put them all into the EHR, you may receive 50 to 100 notifications a day and physicians start ignoring them. The idea is right, but the uncoordinated execution is problematic."

Strategic use of nudges. It is important to design these interventions to fit within clinician workflow, said Dr. Patel. "Stakeholder alignment is key, and clinicians should be involved in their development."

One option for nudges is to work with defaults, which are the path of least resistance and the decision that goes into effect if no action is taken, said Dr. Patel.

To encourage the use of generic medications, for example, the Penn Nudge Unit changed the default in the EHR so that generic medications showed up first in the drop-down menu instead of brands. Generic prescribing quickly increased from 75% to 98%.[1] "When the right choice is clear, health systems can set the default to align with evidence-based guidelines," he said.

"When the right choice is less clear, active choice prompts can be used to remind clinicians to act," said Dr. Patel. However, nudges are powerful, he added, so they should be used carefully, especially when the best choice is sometimes unclear.

1 Patel MS et al. *JAMA Intern Med.* 2016;176(6):847-848.

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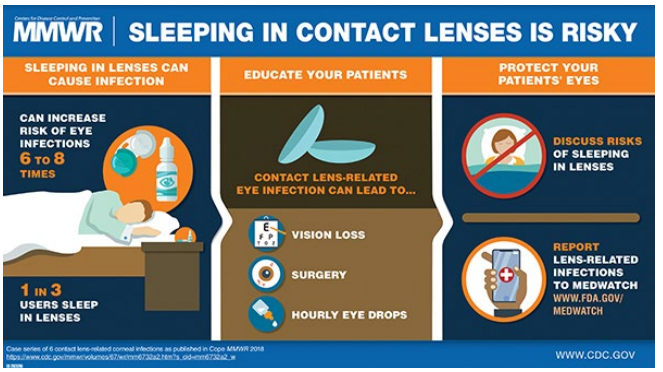


VISUAL ABSTRACTS. *To help quickly relay important study findings, visual abstracts, such as this one, can be useful to physicians and patients.*

Access to information. In addition to volume, information's rapid dissemination through the internet and social media can either facilitate or inhibit the adoption of EBM in medicine, said Dr. Lee. Obviously, the sooner physicians get information the sooner they can integrate it. However, it's not uncommon for one study to contradict the next or for related findings to raise questions or create ambiguity. In the confusion, busy physicians may have trouble determining which new procedures are worth adopting.

Similarly, he said, "patients' access to information may push us to do better faster, or it can create problems, as we've seen with the antivaccine movement."

Practicalities of practice. Cost and medicolegal risk can also affect EBM adoption rates.

Cost. There's no question that real-world practice in ophthalmology is influenced to some degree by billing concerns, said Dr. Sun. "Many of our eye treatments are expensive and rely on specialized care. If the best medicine available requires a $1,000 out-of-pocket expense, what is the best course of action for the patient? The only answer is true informed consent."

Of course, costs can be an issue for physicians and their practices, as well. "Does the new evidence ask physicians to do something different that costs more?" asked Dr. Abbott. "And how will it affect their office and workflow?" For instance, take a practice that does not own a selective laser trabeculoplasty (SLT) machine but wants to offer SLT as primary therapy for primary open-angle glaucoma patients. It could use a machine at an off-site center, but this would significantly alter workflow.

In addition, most payment systems reward volume of procedures rather than outcomes. As a result, adherence to EBM and clinical guidelines may be hindered if payment is not sufficient, Dr. Abbott said.

Medicolegal issues. Exposure to medicolegal risk may factor into adoption of new technology or of drugs that you don't have a lot of experience with, said Dr. Abbott, "If you have a bad or less-than-desirable outcome and you end up in a lawsuit, the prosecuting attorney could argue that you did not take proper steps when adopting the new practice."

Real-world implementation. It can be more difficult to incorporate new protocols into the clinic than in a clinical trial setting, said Dr. Sun. "In planning our clinical trials, we have the luxury of doing what clinicians probably don't, which is to sit down quietly and take the time to look at all the data together."

Additionally, clinical trials may produce impressive results, said Dr. Khurana, but the investigators follow strict protocols and regimens, which don't always translate well into daily practice. "For example, the patient may not want to follow up or be treated as often as the protocol recommends," he said. And other issues may come into play: Perhaps the patient can't afford multiple copays, isn't able to get transportation, or may have a family illness.[5]

In fact, when Dr. Sun sees a referral patient who hasn't responded well to a medication, she first checks whether the dosing regimen has been followed. She has found that inadequate dosing can be a common problem in real-world practice.

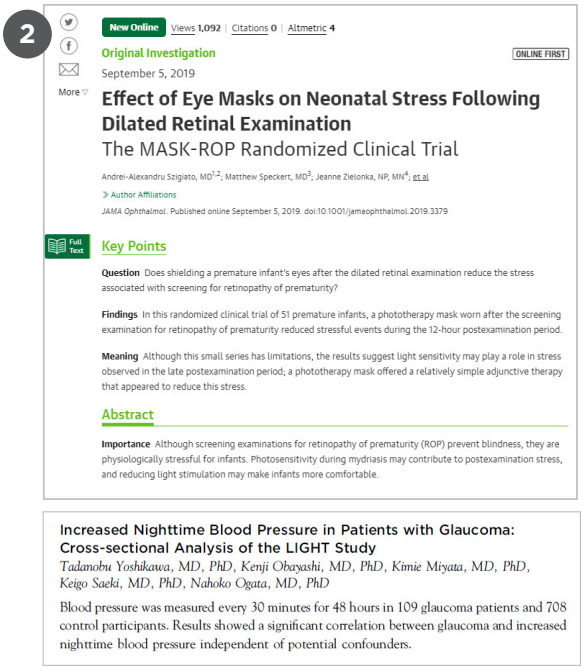
Behavioral Blind Spots

When it comes to adoption of EBM, some barriers may have to do with the behavioral blind spots of both physicians and patients.

Skepticism. "Much Level 1 evidence has been driven by the pharmaceutical or medical device industries attempting to get a new medicine or device approved," said Dr. Khurana. "This can lead to questions about the legitimacy of the data."

Moreover, when evidence goes against our intuition, it's hard to accept and people become very skeptical about it, said Laura Scherer, PhD, an expert in medical decision-making at the University of Colorado, Denver. "Physicians either don't want to incorporate it into practice, or they require a lot more evidence to change what they are doing. They just don't believe that their intuition could be so wrong."

This happens often in medicine, she said, especially when new evidence contradicts practices we hadn't previously tested because we just knew they worked. "Once a clinical trial strongly defies people's expectations, they can have a hard time putting it into practice."



New Online Views 1,092 | Citations 0 | Altmetric 4

Original Investigation ONLINE FIRST

September 5, 2019

Effect of Eye Masks on Neonatal Stress Following Dilated Retinal Examination

The MASK-ROP Randomized Clinical Trial

Andrei-Alexandru Szigiato, MD[1,2]; Matthew Speckert, MD[3]; Jeanne Zielonka, NP, MN[4]; et al

Author Affiliations

JAMA Ophthalmol. Published online September 5, 2019. doi:10.1001/jamaophthalmol.2019.3379

Key Points

Question Does shielding a premature infant's eyes after the dilated retinal examination reduce the stress associated with screening for retinopathy of prematurity?

Findings In this randomized clinical trial of 51 premature infants, a phototherapy mask worn after the screening examination for retinopathy of prematurity reduced stressful events during the 12-hour postexamination period.

Meaning Although this small series has limitations, the results suggest light sensitivity may play a role in stress observed in the late postexamination period; a phototherapy mask offered a relatively simple adjunctive therapy that appeared to reduce this stress.

Abstract

Importance Although screening examinations for retinopathy of prematurity (ROP) prevent blindness, they are physiologically stressful for infants. Photosensitivity during mydriasis may contribute to postexamination stress, and reducing light stimulation may make infants more comfortable.

Increased Nighttime Blood Pressure in Patients with Glaucoma: Cross-sectional Analysis of the LIGHT Study

Tadamobu Yoshikawa, MD, PhD, Kenji Obayashi, MD, PhD, Kimie Miyata, MD, PhD, Keigo Saeki, MD, PhD, Nahoko Ogata, MD, PhD

Blood pressure was measured every 30 minutes for 48 hours in 109 glaucoma patients and 708 control participants. Results showed a significant correlation between glaucoma and increased nighttime blood pressure independent of potential confounders.

JOURNALS. JAMA Ophthalmology *uses Key Points (top), and* Ophthalmology *uses a precis (bottom) to quickly communicate important information to readers.*

Resistance to change. Some physicians see new evidence and say, "Great, when can I sign up for the course?" said Dr. Abbott. "Others tend to be more conservative."

Sometimes it does make sense to wait, said Dr. Lee. "We have to be careful not to jump on a bandwagon too fast. The key is to ask, 'Does this make sense? Are these results truly plausible? Is there a scientific basis for this to work?'"

Dr. Abbott noted that change is more likely if widely publicized, strong evidence confirms that a new approach will result in a significantly improved outcome. Dr. Sun gave an example: DRCR.net Protocol I—a phase 3 study of anti-VEGF medications for DME—showed a dramatic improvement in visual acuity outcomes in the first year with ranibizumab compared to laser alone. This prompted a relatively quick change in clinical practice, she said.

Just *do* something? Physicians and patients are used to thinking that if something doesn't work, they should just do more of it—or if one medicine is good, two are better, said Eve A. Kerr, MD, MPH, at the Ann Arbor Michigan VA Center for Clinical Management Research, and an expert on implementation science. "Sometimes that is not the case," she said. "And once a treatment or practice has been established in medical care, it is much harder to think about how to stop or scale back, particularly because clinical guidelines often don't explicitly address how to do so."

When it's found that a standard practice doesn't really have the desired benefit and instead causes harm, there is still a very strong bias toward continuing with the practice, said Dr. Scherer, who tested a hypothetical scenario posed to both men and women.[7] In her study, participants were told, "Suppose that 30 years of research showed that a breast or prostate test had absolutely no effect on reducing deaths from this particular cancer but did produce harms. Would you want the test?" About half the study participants did, largely because they simply couldn't believe a cancer-screening test wouldn't save lives. Even 43% of those who believed the test wouldn't save their life still wanted it. They were convinced the information would benefit them in some way, even though they weren't sure how, she said.

Racial and gender bias. Although physicians may not admit it, biases may affect consistency of their care. A classic cardiology study conducted at Duke University showed doctors videotapes of patients with identical presenting complaints. "One set of patients were white actors and the other set were black actors," said Dr. Lee. The doctors were asked to assess the patients and make recommendations. The authors wrote, "We found that the race and sex of the patient affected the physicians' decisions about whether to refer patients with chest pain for cardiac catheterization. [This was] even after we adjusted for symptoms, the physicians' estimates of the probability of coronary disease, and clinical characteristics."[8]

Confirmation bias. The process by which people look for information that confirms their view—known as confirmation bias—also may factor into how people interpret EBM.[9] Although there is often good reason to debate about evidence, said Dr. Scherer, we are more likely to question evidence that strongly disconfirms something we want to believe or intuitively believe. "Then it takes much longer and requires much more data to change practice."

Trial Design and Reporting

Certain steps can be taken to enhance trials and speed their translation into clinical practice, said Dr. Kerr.

Encourage community involvement. A major priority of the DRCR.net has been to encourage involvement of both academic centers and community practice physicians, leveraging the strengths of both, said Dr. Sun. "Today, retina specialists in community practice are some of the leading clinical trial investigators throughout the United States, and private practitioners are often more successful at quickly enrolling patients than physicians at academic centers." When community centers are involved from the outset and the

Five Recent Studies Worth Attention

EyeNet asked several editorial board members to suggest papers published within the past year with recommendations that clinicians should consider incorporating into their practices. Here are five that stood out.

Pediatrics

Low-Concentration Atropine for Myopia Progression (LAMP) Study: A Randomized, Double-Blinded, Placebo-Controlled Trial of 0.05%, 0.025% and 0.01% Atropine Eye Drops in Myopia Control.

Half the world's population is expected to be myopic by 2050, greatly increasing the urgency to slow its progression. This trial of 438 children found that low-concentration atropine eye drops reduced myopia progression along a concentration-dependent response. The children tolerated all three concentrations well without an adverse effect on vision-related quality of life.

Yam JC et al. *Ophthalmology*. 2019;126(1):113-124.

Cornea

Descemet Endothelial Thickness Comparison Trial (DETECT): A Randomized Trial Comparing Ultrathin DSAEK With DMEK.

Several large prospective nonrandomized series have suggested similar visual outcomes and rates of rejection between ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK) and Descemet membrane endothelial keratoplasty (DMEK). However, meta-analyses highlighted the need to learn more. In this study, researchers randomized patients to DMEK or UT-DSAEK. They found that DMEK had superior visual acuity results, more rapid recovery, and similar complication rates when compared with UT-DSAEK in patients with isolated endothelial dysfunction.

Chamberlain W et al. *Ophthalmology*. 2019;126(1):19-26.

Retina

Effect of Initial Management With Aflibercept vs Laser Photocoagulation vs Observation on Vision Loss Among Patients With Diabetic Macular Edema Involving the Center of the Macula and Good Visual Acuity: A Randomized Clinical Trial. (Protocol V: DRCR Retina Network)

Intravitreal injections of anti-VEGF agents have been shown to be effective in treating center-involved DME in patients with visual acuity of 20/32 or worse. However, the best approach for center-involved DME with good visual acuity was previously unknown. This study randomly assigned this patient population to either 2.0 mg of intravitreal aflibercept, focal/grid laser photocoagulation, or observation and found no significant difference in vision loss at two years between the three groups.

Baker CW et al. *JAMA*. 2019;321(19):1880-1894.

Retina/Systemic

Management of Acute Retinal Ischemia: Follow the Guidelines!

Despite publication of updated guidelines by the National Stroke Association, the American Heart Association, and the Academy, patients with acute retinal ischemia are rarely evaluated as quickly as those with acute neurologic symptoms. The risk of stroke is highest within the first few days after the onset of visual loss. After performing an ophthalmic exam and making a rapid diagnosis, eye care professionals should immediately refer patients with acute retinal arterial ischemia to the closest emergency department (ED) affiliated with a stroke center without attempting to perform any further testing themselves. Of note, not all EDs have stroke centers.

For more on this topic, see "Retinal TIAs: A Medical Emergency," in the March 2018 EyeNet *at aao.org/eyenet/archive.*

Biousse V et al. *Ophthalmology*. 2018;125(10):1597-1607.

Glaucoma

Selective Laser Trabeculoplasty Versus Eye Drops for First-Line Treatment of Ocular Hypertension and Glaucoma (LiGHT): A Multicentre Randomised Controlled Trial.

Although selective laser trabeculoplasty is a safe alternative to eyedrops for treating primary open-angle glaucoma and ocular hypertension, it is rarely used as a first-line treatment. This randomized controlled trial compared the two approaches, finding that selective laser trabeculoplasty was associated with lower cost, good clinical outcomes, and lower symptom scores, supporting an alternative for primary therapy.

Gazzard G et al. *Lancet*. 2019;393(10180):1505-1516.

realities of practice are taken into account, the chances that the study results can be successfully implemented in practice increase.[10]

Rethink trial design. To make trials more relevant to the challenges of clinical practice, said Dr. Sun, it may help to ask this question: How do we design a trial that will be applicable not only to relatively healthy patients who are highly motivated but also to patients who may not be as motivated or may be sicker, may lack access to medical care, or may not have insurance that is open to specialized care?

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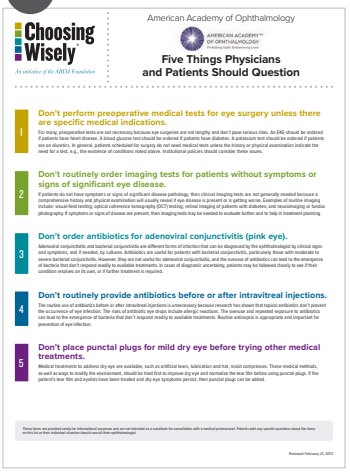
Choosing Wisely
An initiative of the ABIM Foundation

American Academy of Ophthalmology

Five Things Physicians and Patients Should Question

1 Don't perform preoperative medical tests for eye surgery unless there are specific medical indications.

2 Don't routinely order imaging tests for patients without symptoms or signs of significant eye disease.

3 Don't order antibiotics for adenoviral conjunctivitis (pink eye).

4 Don't routinely provide antibiotics before or after intravitreal injections.

5 Don't place punctal plugs for mild dry eye before trying other medical treatments.

CHOOSING WISELY. *This campaign outlines five key areas in which physicians can help patients choose care that is supported by evidence, free from harm, and truly necessary (choosing wisely.org).*

It's also important to remember that no trial can answer every relevant clinical question, said Dr. Sun. "That's why we need to ask, 'What are the questions this study answers well? Which questions are still outstanding? And is it necessary to do another study?'"

Improve outcome reporting. To facilitate translation of research into practice, Dr. Sun noted that it may help to synthesize outcome reporting with tools such as visual abstracts (Fig. 1) and focused tables of contents, which are groupings of, say, five or six of the most important recent studies on specific topic. Over the last decade, the DRCR.net has tried to report outcomes in a way that helps physicians explain results to individual patients. "This means not just providing the average amount of visual acuity change over the course of a trial," said Dr. Sun, "but also trying to report outcomes such as the percentage of patients that gained 2 or 3 lines of vision or who lost vision."

Standardize algorithms. One barrier to EBM adoption that came to light after the initial anti-VEGF studies, said Dr. Sun, was the complexity of the treatment algorithm. "We tried to find ways to articulate the broad philosophy of the algorithm to make it easier for physicians to implement," she said. "For example: Inject into eyes that are improving or worsening but hold the injections once there is sustained stability." Using the same algorithms across multiple studies also helps familiarize physicians with this process.

Obtain more data. Finding more ways to gain data about larger numbers of patients may also be a boon to clinical translation. For example:

Large simple trials. This form of RCT minimizes inclusion and exclusion criteria, making it possible to enroll thousands of people in each arm of the study, said Dr. Lee. "The large sample size allows the investigators to control for confounding variables. When results are unambiguous, uptake may happen more quickly."

IRIS Registry. Comprehensive, large-scale registries provide big pools of data, and, by tracking outcomes, they help confirm uptake of EBM, said Dr. Abbott. Dr. Lee added that registries—such as the Academy's IRIS Registry, which leverages the collective experience of millions of patients around the United States—allow users to see which patterns of care are associated with different outcomes. (See "New Application for IRIS Registry Users.")

Societies and Other Institutions

Education, accessible results, and open dialogue are all key in aiding in adoption of the current evidence, said Dr. Sun. "This is where professional societies can and do play a really strong role, such as with special educational initiatives."

Highlight need-to-know information. For in-

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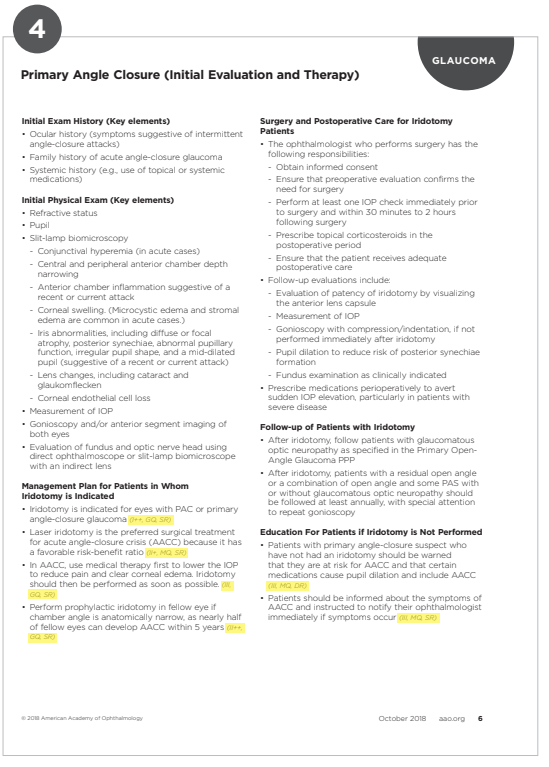

GLAUCOMA

Primary Angle Closure (Initial Evaluation and Therapy)

Initial Exam History (Key elements)
- Ocular history (symptoms suggestive of intermittent angle-closure attacks)
- Family history of acute angle-closure glaucoma
- Systemic history (e.g., use of topical or systemic medications)

Initial Physical Exam (Key elements)
- Refractive status
- Pupil
- Slit-lamp biomicroscopy
  - Conjunctival hyperemia (in acute cases)
  - Central and peripheral anterior chamber depth narrowing
  - Anterior chamber inflammation suggestive of a recent or current attack
  - Corneal swelling. (Microcystic edema and stromal edema are common in acute cases.)
  - Iris abnormalities, including diffuse or focal atrophy, posterior synechiae, abnormal pupillary function, irregular pupil shape, and a mid-dilated pupil (suggestive of a recent or current attack)
  - Lens changes, including cataract and glaukomflecken
  - Corneal endothelial cell loss
- Measurement of IOP
- Gonioscopy and/or anterior segment imaging of both eyes
- Evaluation of fundus and optic nerve head using direct ophthalmoscope or slit-lamp biomicroscope with an indirect lens

Management Plan for Patients in Whom Iridotomy is Indicated
- Iridotomy is indicated for eyes with PAC or primary angle-closure glaucoma (I)++, GQ, SR)
- Laser iridotomy is the preferred surgical treatment for acute angle-closure crisis (AACC) because it has a favorable risk-benefit ratio (BI, MQ, DR)
- In AACC, use medical therapy first to lower the IOP to reduce pain and clear corneal edema. Iridotomy should then be performed as soon as possible. (BI, GQ, SR)
- Perform prophylactic iridotomy in fellow eye if chamber angle is anatomically narrow, as nearly half of fellow eyes can develop AACC within 5 years (I)++, GQ, SR)

Surgery and Postoperative Care for Iridotomy Patients
- The ophthalmologist who performs surgery has the following responsibilities:
  - Obtain informed consent
  - Ensure that preoperative evaluation confirms the need for surgery
  - Perform at least one IOP check immediately prior to surgery and within 30 minutes to 2 hours following surgery
  - Prescribe topical corticosteroids in the postoperative period
  - Ensure that the patient receives adequate postoperative care
- Follow-up evaluations include:
  - Evaluation of patency of iridotomy by visualizing the anterior lens capsule
  - Measurement of IOP
  - Gonioscopy with compression/indentation, if not performed immediately after iridotomy
  - Pupil dilation to reduce risk of posterior synechiae formation
  - Fundus examination as clinically indicated
- Prescribe medications perioperatively to avert sudden IOP elevation, particularly in patients with severe disease

Follow-up of Patients with Iridotomy
- After iridotomy, follow patients with glaucomatous optic neuropathy as specified in the Primary Open-Angle Glaucoma PPP
- After iridotomy, patients with a residual open angle or a combination of open angle and some PAS with or without glaucomatous optic neuropathy should be followed at least annually, with special attention to repeat gonioscopy

Education For Patients if Iridotomy is Not Performed
- Patients with primary angle-closure suspect who have not had an iridotomy should be warned that they are at risk for AACC and that certain medications cause pupil dilation and include AACC (BI, MQ, DR)
- Patients should be informed about the symptoms of AACC and instructed to notify their ophthalmologist immediately if symptoms occur (BI, MQ, SR)

EVIDENCE RATINGS. *The* Summary Benchmarks, *like the* Preferred Practice Patterns (aao.org/ppp), *which they summarize, are accompanied by evidence ratings (yellow).*

stance, to help *JAMA Ophthalmology* readers quickly understand the importance of its studies, the journal began in late 2016 to add "Key Points" (Fig. 2) of 100 words or fewer to its original investigations. Each study article includes one- or two-sentence statements encapsulating these three items: the question under investigation, the finding of the study, and the meaning that readers can take away from the study. Similarly, the *Ophthalmology* journal table of contents includes an approximately 35-word precis summarizing the main findings of each original article, without duplicating the abstract's conclusion.

Target key initiatives. Societies can also help by popularizing key initiatives, said Dr. Khurana, adding that, in fact, this did happen a few years ago. Every specialty society picked a handful of practices that everyone should be doing—they didn't have to be revolutionary. For example, ophthalmologists had typically given patients antibiotic drops after intravitreal injections, but the data showed it didn't demonstrably decrease the risk of infection, he said. This became one of several important deimplementation initiatives of the Academy. Helping to promote this change was Choosing Wisely (Fig. 3), a multispecialty partnership that seeks to prevent the use of unnecessary medical tests, treatments, and procedures.[11]

Simplify guidelines. Given the information overload that clinicians face, synthesis and simplification can make a difference. As secretary for Quality of Care and Knowledge Base Development (2002-2008), Dr. Abbott helped summarize the Academy's approximately 25-page *Preferred Practice Patterns*[12] clinical guidelines for management of various conditions into two-page *Summary Benchmarks* (Fig. 4). The guidelines include an evidence rating. For example, the quality of individual studies is rated on a numerical scale, starting with I++ indicating "High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias." Recommendations for care are based on the body of evidence and are rated starting at "Good quality (GQ). Further research is very unlikely to change our confidence in the estimate of effect." And key recommendations are graded, starting with "Strong recommendation. When the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not."

For a project in China, Dr. Abbott further summarized the benchmarks to create pocket cards, allowing key evidence to "travel" with doctors.

Learn from the VA. The VA is another institution that is helping physicians. Approximately 20 years old, the VA's Quality Enhancement Research

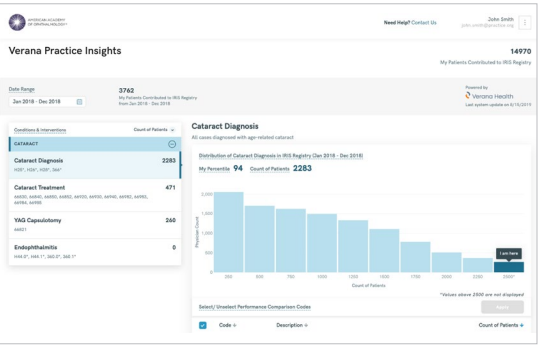
New Application for IRIS Registry Users

Would you like to know how your clinical care compares to that of your peers? This is possible—for cataract surgery, for now—with a new cloud-based app that became available to IRIS Registry users in October. In its initial iteration, the application (called Verana Practice Insights) allows users to:

- examine their own data and trends in patient outcomes and care;
- benchmark individual clinical care patterns against those of other ophthalmologists; and
- visualize deidentified aggregate data of physician practice trends across the United States.

With this information, physicians have a data-based foundation for determining and adopting best practices, improving outcomes, and providing better patient care.

Who will benefit. Verana Practice Insights will initially provide information on practice trends related to cataract surgery and will expand to other indications in early 2020. Those who do not perform cataract procedures but are interested in participating in the future should preregister. This will help determine which areas will be developed next.



CHECK YOUR STATS. *The Verana Practice Insights tool allows cataract surgeons to benchmark their outcomes against those of their peers.*

Who is eligible. Verana Health (www.veranahealth.com) developed Practice Insights for U.S.-based Academy members who participate in the IRIS Registry via an integrated electronic health record (EHR) system. There is no charge.

How to get started. Complete the form at www.veranahealth.com/verana-practice-insights-signup.

Initiative focuses on implementation research and quality improvement. It achieves this by integrating researchers into its system, and they examine all the factors that contribute to adoption of a new technique or, conversely, deimplementation of an obsolete treatment, said Dr. Kerr.

Find implementation funding. "Whether funding comes from internal health systems, insurers, or the NIH, we need more resources to figure out what works and what doesn't and to do larger-scale implementation research," said Dr. Kerr. "We put a lot of funding into new discoveries, but very little into making sure they get to the right people at the right time."

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12 aao.org/preferred-practice-patterns.

Meet The Experts

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See disclosure key, page 8. **For full disclosures,** view this article at aao.org/eyenet.

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INDICATIONS AND USAGE

DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a topical corticosteroid that is indicated for:

- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

Dosage and Administration

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

- *Intraocular Pressure (IOP) increase* – Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- *Cataracts* – Use of corticosteroids may result in posterior subcapsular cataract formation.
- *Delayed Healing* – The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- *Bacterial Infections* – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- *Viral Infections* – Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- *Fungal Infections* – Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- *Contact Lens Wear* – DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Most Common Adverse Reactions

- In postoperative ocular inflammation and pain studies, ocular adverse reactions occurring in 5-15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.
- In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.

For additional information about DUREZOL® Emulsion, please see Brief Summary of Prescribing Information on adjacent page.

***Terms and Conditions:** Limitations apply. Eligible, commercially insured patients may pay as little as $30 in out-of-pocket expenses for each 5-mL bottle of DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, with a maximum benefit per bottle of $155. This offer is not valid under Medicare, Medicaid, or any other federal or state program. For additional information, please visit www.copay.novartispharma.com.

References: 1. Durezol [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2017. **2.** Stringer W, Bryant R. Dose uniformity of topical corticosteroid preparations: difluprednate ophthalmic emulsion 0.05% versus branded and generic prednisolone acetate ophthalmic suspension 1%. *Clin Ophthalmol.* 2010;4(1):1119-1124. **3.** Korenfeld MS, Silverstein SM, Cooke DL, Vogel R, Crockett RS; Difluprednate Ophthalmic Emulsion 0.05% (Durezol) Study Group. Difluprednate ophthalmic emulsion 0.05% for postoperative inflammation and pain. *J Cataract Refract Surg.* 2009;35(1):26-34. **4.** Fingertip Formulary, January 2018.

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5/19

T-DZL-1374355

DUREZOL® (difluprednate ophthalmic emulsion) 0.05%
Initial U.S. Approval: 2008

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

1.1 Ocular Surgery

DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.

1.2 Endogenous Anterior Uveitis

DUREZOL is also indicated for the treatment of endogenous anterior uveitis.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Intraocular pressure (IOP) Increase

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

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 Bacterial Infections

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

5.5 Viral Infections

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

5.6 Fungal Infections

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

5.7 Topical Ophthalmic Use Only

DUREZOL is not indicated for intraocular administration.

5.8 Contact Lens Wear

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

6 ADVERSE REACTIONS

The following serious reactions are found elsewhere in the labeling:

- Elevated IOP *[see Warnings and Precautions (5.1)]*
- Posterior subcapsular cataract formation *[see Warnings and Precautions (5.2)]*
- Secondary ocular infection *[see Warnings and Precautions (5.4)]*
- Perforation of the globe *[see Warnings and Precautions (5.3)]*

6.1 Ocular Surgery

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

6.2 Endogenous Anterior Uveitis

A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL. The most common adverse reactions of those exposed to DUREZOL occurring in 5% to 10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2% to 5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects

Pregnancy Category C

Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal anomalies) when administered subcutaneously to rabbits during organogenesis at a dose of 1-10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL, since DUREZOL is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

8.3 Nursing Mothers

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

8.4 Pediatric Use

DUREZOL was evaluated in a 3-month, multicenter, double-masked trial in 79 pediatric patients (39 DUREZOL; 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL to prednisolone acetate ophthalmic suspension, 1%.

8.5 Geriatric Use

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

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April 2017

Why Your Ophthalmology Colleagues Were in the Auditors' Crosshairs

What do auditors zero in on? Visit aao.org/audits for a list of target areas, plus resources for each of them. Recently, ophthalmology practices have been audited on the following issues.

Intravitreal injections. In 2019, Novitas, a Medicare Administrative Contractor (MAC), started targeting practices that use a high volume of aflibercept (Eylea) and/or ranibizumab (Lucentis) and subjecting them to a prepayment Target, Probe, and Educate (TPE) audit on up to 40 records. The Academy sent an alert to all members within Novitas' jurisdiction; this alerted them to the issue and reminded them to use the Academy's checklist of documentation requirements (see this article online at aao.org/eyenet). Most physicians passed the audits. Of those who didn't initially pass, documentation problems included no record of visual acuity (VA), nothing to support why a particular drug was used, no mention of how the patient is doing on the drug, and no notation of residual medication wasted. (Novitas is the MAC for the District of Columbia, Arkansas, Colorado, Delaware, Louisiana, Maryland, Mississippi, New Jersey, New Mexico, Oklahoma, Pennsylvania, and Texas.)

Eye visit codes. The Academy also heard from some practices that had been submitting a high volume of Eye visit codes; upon audit, they were down-coded from comprehensive new and established patient exams (CPT codes 92004 and 92014, respectively) to intermediate new and established patient exams (92002 and 92012). Why? The auditor had erroneously applied the documentation requirements for the E&M codes. Once the auditors were educated about this, either the audit result was dismissed or only a small percentage of submissions were down-coded. Why were a few still down-coded? In those instances, the practice hadn't performed and documented all 12 elements of the exam.

Upper lid blepharoplasty. Blepharoplasty audits don't happen as often as they used to, but auditors do still sometimes target CPT code 15823 *Blepharoplasty, upper eyelid; with excessive skin weighting down lid.* Why is payment denied? In some cases, practices had cloned the chief complaint verbatim from one patient's record to the next; in others, the auditors said that the chief complaint was more cosmetic than functional in nature.

Blepharospasm Botox injections. If you are billing for a drug that came in a single-use vial, Medicare requires that you use modifier –JW to report wastage. However, payers that don't follow Medicare's rules might not require it. Indeed, some practices have found that use of –JW for non-Medicare patients triggered audits. In several of these cases, the audits revealed that practices were using Botox vials packaged for cosmetic—not functional—treatment.

Cataract surgery. Why have cataract surgeons failed audits of their documentation? Common reasons include: No documentation of best-corrected VA; cutting and pasting the same activity-of-daily-living complaints into the records of multiple patients; and no notation that the patient desires to proceed with surgery.

Complex cataract surgery. You may trigger an audit if 10% or more of your cataract surgeries are billed as complex (CPT code 66982). And you will fail that audit if you don't meet the MAC's documentation requirements for code 66982, even if the surgeries were in fact complex. To find those documentation guidelines, see your MAC's local coverage determination(s) for cataract surgery at aao.org/lcds. (Note: 66982 is on the list of prepayment TPE audits.)

What about the commercial audits? While Medicare Part B MACs consider the use of dye for the mature cataract a qualification of complex cataract surgery, many commercial payers may not. You must not take one payer's rule and apply it to all payers.

Extended and subsequent ophthalmoscopy. Claims for extended ophthalmoscopy (CPT code 92225) have been denied because the documentation didn't note scleral depression or the diopter of lens that was used, or the drawings lacked sufficient labeling or detail. Claims for subsequent ophthalmoscopy (92226) have been denied when no change was noted from the last exam.

BY **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT.

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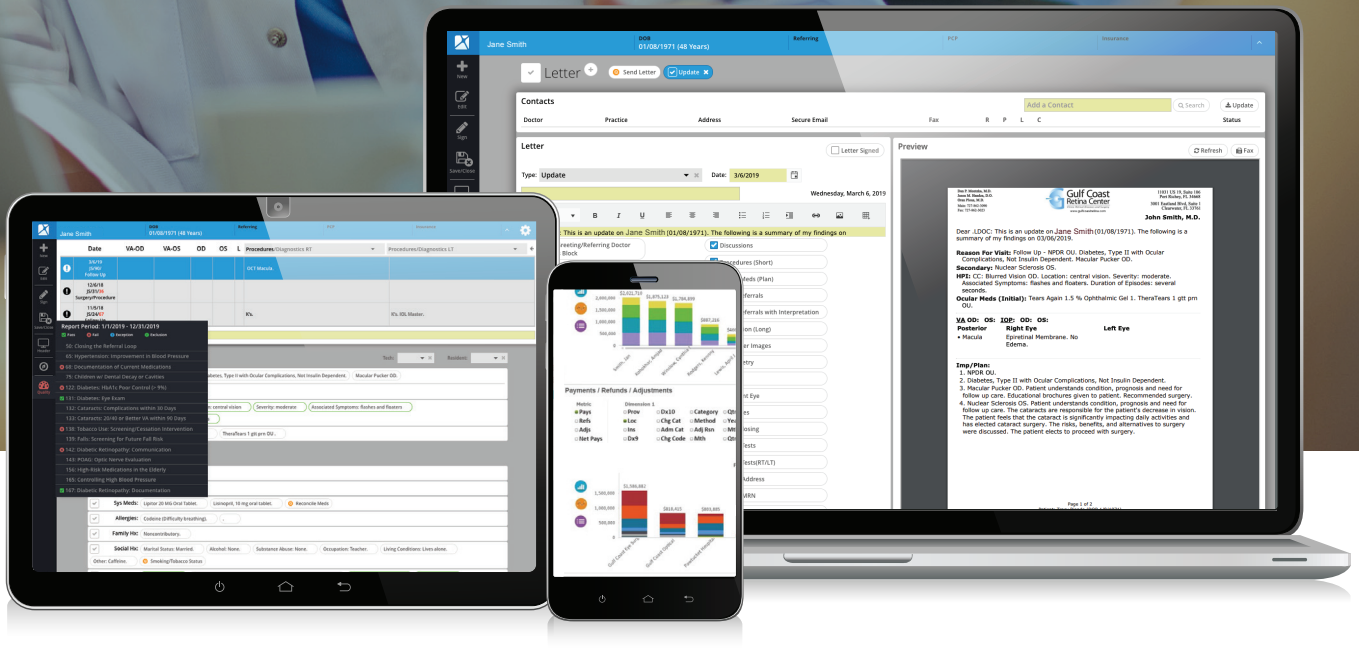

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Alternatives to Private Equity for Ophthalmology Practices

A growing number of ophthalmology practices are weighing the pros and cons of selling to a private equity firm, and the benefits may be mixed (see November's cover story, "Private Equity and Ophthalmology: Explore Your Options, Beware the Hazards" at aao.org/eyenet/archive).

Alternatives to Private Equity

Physicians who don't want to sell their practice to a private equity firm "may still see the need to consolidate as a way to compete in a changing marketplace," said Derek A. Preece, MBA, a consultant in Orem, Utah. "For these ophthalmology practices, there are some viable alternatives."

1. A merger of practices. In this model, two or more practices merge into one entity. Typically, the physicians who had been owners of the individual practices become owners of the combined group, said Mr. Preece.

Economies of scale. Gary I. Markowitz, MD, president and CEO of SuperVision Advisors, said this alternative creates a working model that early- and mid-career ophthalmologists may find preferable to private equity because the new, combined practice can:

- reduce operating costs, including those relating to human resources, such as payroll expenses;
- negotiate better purchasing prices;
- negotiate higher reimbursement from payers (where possible); and
- free up physician time for clinical work that will generate more revenue.

Must be willing to compromise. Mr. Preece cautioned that merging multiple practices can be difficult because practices operate differently and have different cultures and values. If the merger is going to be successful, some aspects of each participating practice may have to change, but the logistics of getting physicians to agree on all aspects of the merger can be "extremely arduous," said Dr. Markowitz.

Expect headaches. Mr. Preece cited a simple illustration: the merger of two practices that have different computer systems. "One of the two practices usually needs to adopt the software of the other, which can cause a lot of work and headaches for the practice that switches," said Mr. Preece. "I do know of a practice that was able to find a way to allow the different merger partners to maintain their own computer systems by installing a software bridge, but that required a significant amount of work."

It can take time for the benefits to materialize. While efficiencies eventually can be realized with the merger model, it takes time to reach this stage and usually requires a long-term strategy to physically integrate on a more comprehensive level, Dr. Markowitz added.

One example of a successful merger is Vantage EyeCare (see next page).

2. A merger, plus a third-party administrator. Multiple practices merge and hire a third-party administrator who runs the practice while the physicians retain control. "This is a model we find in the plastic surgery field," said Dr. Markowitz. "A third party sets up a turnkey operation for the newly merged entity."

3. Acquisition by another practice. "In this model, the owners of the acquired practice are often close to retirement and want to divest the practice," said Mr. Preece.

How is this different from a private equity buyout? Most private equity firms want to resell their acquired practices within three to five years. This means new owners and often new management of the company for whom the physicians are working. By contrast, if a physician-owned practice acquires your practice, there is more likely to be long-term continuity.

On the other hand, physician-owned practices "don't typically pay the high multiples of EBITDA [earnings before interest, taxes, depreciation and amortization] that a private equity firm will pay," Mr. Preece noted.

4. Acquisition by a hospital or academic group. In this model, the owner becomes an employee, said Mr. Preece. "In most cases, the hospital purchases the practice at a price that is based on the value of the equipment and other hard assets only. They don't pay for the cash flow, EBITDA, or good will. Consequently, the purchase price will be lower."

Physician wages may be based on collections or work RVUs. Dr. Markowitz added that wages paid to physicians

BY LORI BAKER-SCHENA, MBA, EDD, INTERVIEWING **JULIA LEE, JD, GARY I. MARKOWITZ, MD,** AND **DEREK A. PREECE, MBA.**

in this model are sometimes based upon collections, and the collection rate may be higher than in the physician-owned practice, as hospitals often can negotiate better payment rates. In other situations, hospitals pay doctors based on the work RVUs (relative value units) they produce without regard to collections, said Mr. Preece.

Avoid the headaches of running a practice. Dr. Markowitz said this model is particularly attractive to those who seek to deliver quality medicine but may not want the responsibility that comes with running a practice.

You might like this option, but does this option like you? Interestingly, Mr. Preece added, while some ophthalmology practices have been sold to hospitals in the past five to 10 years, it is not as common as with other specialties because ophthalmologists "don't put many patients in hospital beds."

5. Acquisition by a multispecialty physician firm. Dr. Markowitz noted that a buyout by a medium- to larger-sized multispecialty group can be compared to being acquired by a hospital and has similar advantages.

"If you get into some of the smaller multispecialty entities, however, there may be the opportunity to have more control and maybe even get the opportunity to establish an equity ownership position," Dr. Markowitz said.

6. Staying independent. "If the practice is doing well financially, satisfying the needs of patients and physicians, and there isn't any imminent threat to the practice in the marketplace, the owners may decide to remain independent," said Mr. Preece.

Consider your options. Before assuming that you must sell to private equity, consider the alternatives. Whatever the decision, said Dr. Markowitz, it is crucial to "do your research." Rigorous due diligence is necessary to assess any of these alternatives.

Ms. Lee is chief executive officer of Vantage Eye Care in the Philadelphia metropolitan area. *Financial disclosures: Modernizing Medicine: C; Vantage EyeCare: E.*

Dr. Markowitz is director emeritus at Delaware Eye Center and Blue Hen Ambulatory Surgical Center in Dover, Del., and is president and CEO of SuperVision Advisors, which is based in Wilmington, Del. *Financial disclosures: SuperVision Advisors: C,O.*

Mr. Preece is a principal and executive consultant with BSM Consulting, which is based in Orem, Utah. *Financial disclosures: BSM consulting: E.*
See disclosure key, page 8.

FURTHER READING. The AAOE curates a select list of private equity articles at aao.org/practice-management/private-equity.

Vantage EyeCare: A Physician-Owned Alternative to Private Equity

Based in the Metro Philadelphia region, Vantage EyeCare is the largest private physician-owned ophthalmology group in the country, said its CEO, Julia Lee, JD.

How it started. "In 2017, ophthalmologists from five practices came together to explore a collective sale to a private equity firm," Ms. Lee recalled. "My group, Ophthalmic Partners, was not part of the initial discussion as we had earlier decided private equity was not the optimal path for our multigenerational practice.

"At the 11th hour," she continued, "these five practices decided not to move forward with private equity as it would have changed their culture significantly."

A tight timeline. They then called a meeting with four additional groups, and the nine groups expressed a desire to integrate into a single practice—forming a steering committee in February 2017 with a very tight timeline: 11 months. In that time, the committee had to:

- select a name and logo, trademark it, and incorporate the new entity;
- draft all governing documents and approve a budget;
- establish employee benefits and a 401K program;
- get malpractice and corporate insurance policies;
- select and implement a practice management bridge;
- select and implement a payroll platform; and
- engage a credentialing company and other key vendor partners.

"We met every other Monday night to make these operational decisions," Ms. Lee said. "It was a big commitment, but we all believed in what we were doing."

Launched in January 2018. Vantage EyeCare ultimately launched with seven divisions (representing seven of the original practices) and 45 physicians. At the one-year mark, it had more than doubled in size. And it now has approximately 120 providers and 16 previously free-standing practices merged under a single Tax Identifier Number (TIN).

The secret to this successful merger? Ms. Lee thought the following factors were key to the practice's success:

- Shared beliefs created a strong foundation. Former friendly competitors came together and were able to work collaboratively and intensely toward a common goal.
- Doctors hired a CEO and chief operations officer (COO) who had run two of the larger practices that joined Vantage EyeCare, enabling efficient operationalization.
- Physicians were willing to invest time and resources.
- Physicians were willing to compromise on a variety of issues as the formation of the new group unfolded.

The practice today. "We are now at the point that we don't want to grow simply for the sake of becoming larger. Instead, we want our growth to be more strategic," said Ms. Lee. "We launched, we grew, and now we have this scale that allows us to take advantage of initiatives including formal coordination with primary care networks. Unlike private equity firms, which invest in practices because they intend to extract or liquidate value at some point, we are interested in growing value for the sake of better patient care. This is our driver. It is the common goal that will make a difference five years from now."

Academy Notebook

NEWS • TIPS • RESOURCES

STAR AWARDS. *The Texas Ophthalmological Association (TOA) was awarded a 2019 State Affairs Star Award during AAO 2019 for its Safe Vision Texas Coalition—The Right Eyecare for All Texans. From left to right: Sidney K. Gicheru, MD, past TOA president (2014-2015); Jeremiah Brown, MD; John M. Haley, MD, past TOA president (2017-2018); Robert D. Gross MD, Academy councilor for TOA; Rachael Reed, CAE, TOA executive director; Mark J. Gallardo, MD, TOA president; and Kurt F. Heitman, MD, Academy Secretary for State Affairs.*

WHAT'S HAPPENING

State Societies Honored During AAO 2019

The Academy Secretariat for State Affairs recognized two societies with its 2019 Star Award at the Oct. 14 State Society Presidents' Breakfast & Recognition Awards during AAO 2019. The Star Award program provides special recognition to state ophthalmology societies for outstanding efforts on programs or projects they have implemented in the previous year. The winning societies are:

Illinois Society of Eye Physicians and Surgeons for its Patients as Advocates for Safe Surgery project. The society successfully engaged patients as advocates in their ongoing effort to preserve quality eye care in Illinois.

Texas Ophthalmological Association for its Safe Vision Texas Coalition—The Right Eyecare for All Texans. The society established and mobilized a coalition of patients and physicians in support of efforts to ensure all Texans receive the right eye care by the right professional.

Since the Star Award program's inception in 2001, the Secretariat for State Affairs has recognized 69 state ophthalmology society programs with the award. State ophthalmology societies may apply for this award by responding to the Secretariat for State Affairs' annual organizational survey of state societies, which goes out in late spring or early summer.

State Society Executive Directors Recognized for Outstanding Contributions

Each year, the Academy Secretariat for State Affairs publicly acknowledges state ophthalmology society executive directors for their contributions to their state societies and for their partnership and collaboration with the Academy on its national efforts. During AAO 2019 in San Francisco, the Secretariat recognized executives of two state ophthalmology societies for their exemplary work.

2019 Outstanding Executive Director: Organizational Development—Maura Campbell, Executive Director, Michigan Society of Eye Physicians and Surgeons (MiSEPS), for her efforts to improve the organizational strength of MiSEPS, notably leading the society's rebranding efforts, which included developing a strategic communications plan and launching a new society web site.

2019 Outstanding Executive Director: Political Action—Sheila Bush, Executive Director, Wyoming Ophthalmological Society (WOS), for orchestrating the efforts of the WOS to defeat optometric surgery legislation.

The Academy Secretary for State Affairs, **Kurt F. Heitman, MD,** praised the efforts of all executive directors on behalf of state societies and ophthalmologists across the country. "State society executive directors are vital

AMERICAN ACADEMY OF OPHTHALMOLOGY®

members of ophthalmology's team who are committed to serving our profession and our patients. We in State Affairs appreciate their expertise, respect their dedication to preserving quality eye care, and value their partnership in addressing the needs of our members."

TAKE NOTICE

Nominate a Colleague for the Laureate Award

Every year, ophthalmologists distinguish themselves and the profession by making exceptional scientific contributions toward preventing blindness and restoring sight worldwide. The Academy Board of Trustees will recognize these extraordinary contributions with its Laureate Award, the Academy's single highest honor. The award recipient is announced each fall, and the Laureate is recognized during the Opening Session of the annual meeting.

Nominate a colleague using the application at aao.org/laureate by Jan. 31, 2020.

Submit Your Research to *Ophthalmology*

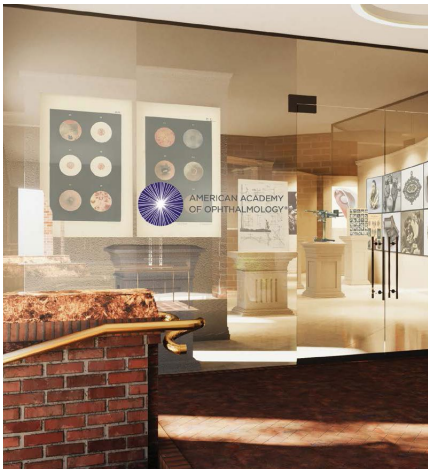
Ophthalmology is the flagship journal of the Academy. With a 7.7 Impact Factor and a print circulation of 27,000 subscribers, you can reach a broad audience. Submit your research today!

Submit a manuscript at www.editorialmanager.com/ophtha.

MIPS: Dec. 31 Deadline for EHR Hardship Exceptions

In the Merit-Based Incentive Payment System (MIPS), the performance category that reports use of electronic health records (EHR) is called promoting interoperability (PI). It is one of four MIPS performance categories and contributes up to 25 points to your MIPS final score (0-100 points). Under normal circumstances, when you report no PI measures, your PI score is zero and your maximum MIPS final score is 75 points.

The significant hardship exception. However, you can apply to be exempted from PI if you are facing a significant hardship—for example, losing access to your EHR system because of extreme



HOLIDAY GIVING. *Make a gift to the Academy Foundation in honor or memory of a mentor, colleague, or family member. Your funds will support Academy programs, including the Truhlsen-Marmor Museum of the Eye. Make your gift by Dec. 31 to receive the tax deduction for 2019. Donate at aao.org/foundation/giving-options.*

circumstances that are beyond your control, such as a fire, severe financial distress, or vendor issues.

If the Centers for Medicare & Medicaid Services (CMS) accepts your application for a hardship exception, PI's contribution to your final score will be reweighted to zero, and the quality performance category's contribution will be reweighted upward; thus, you could still earn the maximum MIPS final score of 100 points despite not reporting PI measures.

Special consideration given to small practices. If small practices can demonstrate that obtaining and maintaining certified EHR technology would cause undue hardship, CMS may grant them a PI hardship exception.

Submit your application by Dec. 31, 2019. For guidance on submitting this application and examples of significant hardships, see aao.org/medicare/promoting-interoperability/exceptions.

MIPS: Your EHR Must Be 2015-Certified by Dec. 31

Check your electronic health record (EHR) system's certification. To check whether your EHR system is a 2015-edition CEHRT, visit https://chpl.healthit.gov/#/search.

Your EHR certification impacts how you report quality. If your EHR system doesn't have 2015-edition certification by the end of the year, the IRIS Registry *may* still be able to extract quality measure data from your EHR. However, your scores would be based on the measure benchmarks used for manual reporting, many of which are subject to significant scoring limitations, and you would not be able to claim the bonus for end-to-end electronic reporting. You also would be able to report only measures that are available for manual reporting, which means you would not be able to report measure 318: Falls: Screening for Future Fall Risk.

What about promoting interoperability (PI)? Having 2015-edition functionality throughout your PI performance period and having 2015-edition certification by the end of your performance period are prerequisites for PI reporting. If your EHR vendor isn't able to provide you with both, apply for a hardship exception (see this page).

MIPS: Jan. 31 Deadline for IRIS Registry Reporting

Don't wait until the last minute. By Jan. 31, 2020, those who use the IRIS Registry for MIPS reporting will need to do the following:

1. Finish manual reporting for 2019. This includes quality measures, promoting interoperability (PI) measures, and improvement activities. When manually reporting data for quality measures, you can either enter patients one at time or enter them as a batch via a properly formatted CSV file. If you successfully integrated your EHR with the IRIS Registry, your MIPS quality data are automatically extracted, but you can only report PI measures and improvement activities manually.

Include the data-completeness totals. If you are manually reporting patients for a quality measure, you must submit to the IRIS Registry the total number of patients eligible and excepted from that measure.

If you report a quality measure on fewer than 100% of patients, do not cherry-pick. When you submit your MIPS quality data to CMS, you must

certify that, to the best of your knowledge, your data is "true, accurate, and complete." In the Aug. 14, 2019, edition of the *Federal Register,* CMS clarified that if you report on a measure for fewer than 100% of applicable patients, you should not select patients with the goal of boosting your performance rate; the agency states that such "cherry-picking" would result in data that is not "true, accurate, and complete."

2. Submit a signed data-release consent form. The IRIS Registry won't submit a provider's MIPS data to CMS unless it has received the signed consent form. Providers who are reporting as individuals should sign their own consent forms; providers who are reporting as a group can be included on a single consent form, which can be signed by the administrator. All your practice's ophthalmologists must be up to date with their 2019 Academy membership dues. You must submit a new consent form each year and can do so via the IRIS Registry dashboard. For instructions, see aao.org/consent-form.

Learn more about the IRIS Registry and MIPS at aao.org/iris-registry and aao.org/medicare.

ACADEMY RESOURCES

View the Latest Guidelines

The Academy's *Ophthalmic Technology Assessments* evaluate new and existing procedures, drugs, and diagnostic and screening tests for safety and clinical effectiveness. Review the current assessments:

- *The Effect of Anti-Vascular Endothelial Growth Factor Agents on Intraocular Pressure and Glaucoma,*
- *Use of Orthokeratology for the Prevention of Myopic Progression in Children,* and
- *Intraocular Lens Implantation During Early Childhood.*

Find assessments at aao.org/ota.

Register Now for Ophthalmology's Most Important 2020 Coding Update

Start the new year by proactively protecting your patients and your practice. The Academy's 2020 Ophthalmology Coding Update, presented by David B. Glasser, MD, Academy Secretary for Federal Affairs, and Sue Vicchrilli, Academy Director of Coding and Reimbursement, will detail critical updates to the cataract/glaucoma combined procedure, the new family of extended ophthalmoscopy codes, the CCI edits, and more. Plus, they will preview the new E&M guidelines for 2021. This recorded presentation is eligible for CME credit and will be available on Jan. 8, 2020.

Preorder your access today at aao.org/2020coding.

D.C. REPORT

CMS Finalizes ASC Burden-Reduction Strategy, Academy Nets Advocacy Win

The Centers for Medicare & Medicaid Services (CMS) is following through with a strong plan to eliminate obsolete administrative requirements, this time benefiting ambulatory surgery centers (ASCs) and their patients.

No pre-op exams requirement. The Academy in December 2018 urged CMS to drop the requirement for comprehensive preoperative physical examinations, which are irrelevant to eye surgery. In a final rule that takes effect in 2020, the agency eliminates this requirement, replacing it with one that offers ASCs greater flexibility to determine which patients and surgeries are low risk. The agency advanced this plan as part of its ongoing Patients Over Paperwork initiative, which strives to eliminate barriers between physicians and those seeking care.

The Academy endorsed this plan because it would allow ASCs to create their own policies for presurgical medical histories and physical examinations, including associated testing.

In its new policy, CMS is taking the following steps:

- It is finalizing the proposal to revise the comprehensive preoperative physical examinations requirement to state, "Significant medical history and results of physical examination, as applicable."
- It is finalizing the proposal to eliminate the requirement for each patient to have a medical history and physical assessment completed by a physician not more than 30 days before the scheduled surgery and replace it with the requirement for ASCs to develop and maintain a policy that identifies those patients who require a medical history and physical examination prior to surgery.
- It is revising current policy to clarify that the ASC rules must be based on nationally recognized standards of practice and guidelines and applicable state and local health and safety laws.

The policy is consistent with the Academy's Choosing Wisely initiative, by which the Academy supports eliminating preoperative medical tests for eye surgery unless there are specific medical indications. In fact, when issuing its draft rule, CMS cited cataract surgery and Nd:YAG capsulotomy among its primary motivators for this change.

No hospital arrangements requirement. CMS is also eliminating another requirement opposed by the Academy, which required facilities to either have a written transfer agreement with a hospital or ensure that all physicians have admitting privileges in a hospital. The agency has instead decided that it will require ASCs to periodically provide the local hospital with written notice of its operation and patient population served. Many ambulatory surgery center owners have told the Academy that it is difficult to secure these arrangements from hospitals. Lacking the transfer agreement or admitting privileges sometimes caused ASCs to fail Medicare's compliance requirements.

Attend the Ophthalmology Business Summit, March 14-15, 2020

The Academy's leadership-focused Ophthalmology Business Summit in Chicago offers the tools and tactics you need to nurture a thriving, successful ophthalmic practice. As shifting regulations and market forces continue to produce uncertainty, it's more important than ever to actively address the complex business challenges impacting your practice's health and viability. Physician leaders and senior administrators who attend as a team can take full advantage of the all-new curriculum.

Learn more and register at aao.org/business-summit.

Get 10% Off Patient Education Brochures Until Dec. 31

Don't leave patients self-diagnosing with "Dr. Google." Send them home with easy-to-understand, ophthalmologist-reviewed brochures from the Academy to save time and mitigate risk. Now through Dec. 31, get 10% off when you use code PEB2019. No minimum purchase is required to take advantage of this time-limited offer.

Order today by visiting aao.org/patientbrochures.

MEETING MATTERS

2020 Abstract Deadlines

Want to create content for AAO 2020 in Las Vegas? Submit your ideas for an instruction course or new Skills Transfer lab. Abstracts will be accepted from Dec. 12, 2019, through Jan. 14, 2020.

Learn more at aao.org/presentercentral.

Submit a 2020 Practice Management Course

Each year, the AAOE offers a wide range of new courses as part its practice management program that runs in parallel with the Academy's annual meeting. These sessions address current practice management challenges, coding issues, and more. Do you have a great idea for a course? Submit an instruction course abstract between Dec. 12, 2019, and Jan. 14, 2020.

To submit, visit aao.org/abstracts. **For more information,** contact Licia Wells, AAOE Program Manager, at lwells@aao.org.

Claim CME for AAO 2019

If you attended AAO 2019 and/or Subspecialty Day and your attendance was verified onsite in San Francisco, you should have received an email with a link and instructions for claiming CME credits online. You can claim credits (if you did not already do so at the meeting) and obtain transcripts that include AAO 2019/Subspecialty Day credits at CME Central. The Academy transcript will not list individual course attendance, only overall credits claimed.

Claim credits at aao.org/cme-central. **For more information,** visit aao.org/annual-meeting/cme.

View the Virtual Meeting

The Virtual Meeting is a free online component of AAO 2019. View 18 archived sessions from San Francisco (approximately 25 hours of educational content) through Jan. 31, 2020. Access the Virtual Meeting with your Academy login and password. The AAO 2019 Virtual Meeting cannot be reported for CME credit.

For more information, visit aao.org/virtual-meeting.

Enjoy AAO 2019 All Year

AAO 2019 Meetings on Demand provides recorded presentations from the San Francisco meeting and is available in several configurations. The AAO 2019 Complete Package includes all recorded programming: content from the seven Subspecialty Day meetings, the AAOE Practice Management Program, and highlights from AAO 2019. Nearly 200 hours are included. You can also purchase individual Subspecialty Day meetings, just the AAO 2019 Highlights, or only the AAOE Practice Management Program.

Learn more at aao.org/ondemand.

MEMBERS AT LARGE

Troutman Prizes

Troutman Cornea Prize for Young Clinician Investigators. This award, established by a Castroviejo Cornea Society Founder, Richard C. Troutman, MD, DSc (Hon), is awarded annually to the investigator under 41 years of age who authored the best paper published in *Cornea* the year before.

This year's recipient is **Marina Bertolin, MSc,** of the Fondazione Banca degli Occhi del Veneto in Italy, for her paper, "Optimized Protocol for Regeneration of the Conjunctival Epithelium Using the Cell Suspension Technique." Ms. Bertolin was awarded a $5,000 honorarium from the Troutman Endowment and had the opportunity to present her work at the annual scientific meeting of the Cornea Society, which took place prior to AAO 2019.

Ms. Bertolin

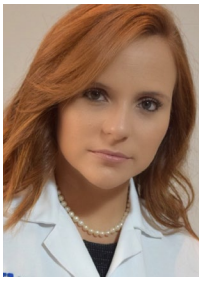
"Receiving this award is tremendously satisfying for all of us at the Fondazione Banca degli Occhi del Veneto who have worked on this project," said Ms. Bertolin.

"Over the past two decades, our group in Venice has worked toward the development of a treatment for patients with limbal stem cell deficiency. The grafts prepared in our GMP Factory have been transplanted onto over 200 patients. Such experience suggested that stem cell therapy could become a potent and valuable therapeutic tool in clinical practice.

"Therefore, a few years ago, we thought it would seem plausible that even transplants of autologous conjunctival epithelial sheets, generated by ex vivo cultured conjunctival stem cells, could represent an appropriate therapeutic option for conjunctival diseases refractory to current therapies. As a matter of fact, every year more than 1,000 patients in Italy and more than 100,000 worldwide develop severe disorders of the ocular surface in general and of the conjunctiva in particular. This led our group to set up a collaborative effort with the University of Padova and Verona in Italy and the University of Antwerp in Belgium to identify where conjunctival stem cells

were located and how we could isolate and culture them to obtain grafts of clinical transplantable grade. The next step that we are working on is to move our findings onto a clinical setting."

Richard C. Troutman, MD, DSc (Hon) Prize. This prize is awarded on behalf of the International Society of Refractive Surgery to a young author published in the *Journal of Refractive Surgery.*



Dr. Medeiros

This year's recipient is **Carla Santos Medeiros, MD, PhD,** a postdoctoral fellow in refractive surgery and cornea at Cole Eye Institute at the Cleveland Clinic Foundation and head of Refractive at Santa Casa da Misericórdia in Rio de Janiero, Brazil. Her paper, "The Impact of Photorefractive Keratectomy and Mitomycin C on Corneal Nerves and Their Regeneration," discusses new histological findings that provide insight into neural remodeling processes after corneal refractive surgery. Dr. Medeiros received a $5,000 honorarium from the Troutman Endowment and presented an honorary lecture during Refractive Surgery Subspecialty Day 2019.

Dr. Medeiros said, "Receiving the Troutman Award is a true honor for both myself and our team at the Cole Eye Institute. We look forward to more opportunities to further investigate the wound-healing response process after refractive surgery."

Suzanne Véronneau-Troutman Award. The Suzanne Véronneau-Troutman Award, established by Suzanne Véronneau-Troutman, MD, FRCS(C), FACS, and awarded annually by Women in Ophthalmology (WIO), recognizes an ophthalmologist who has done the most in the preceding year to advance and enhance the position of women in ophthalmology.

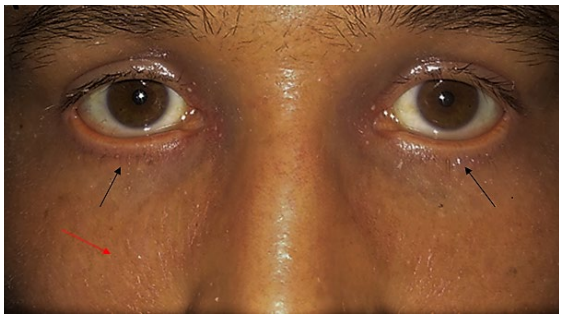
This year, at the WIO Reception and Awards Ceremony held during AAO 2019 in San Francisco, this award was presented to **Judy E. Kim, MD,** who is professor of ophthalmology at the Medical College of Wisconsin in Milwaukee.

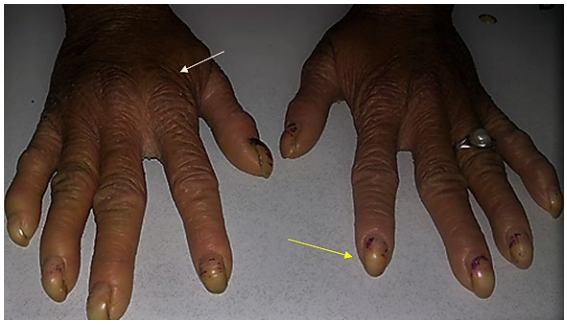
Dr. Kim has worked tirelessly to enhance and improve the professional environment of women ophthalmologists through her many leadership roles that provide unparalleled opportunities and platforms to influence, support, and speak on behalf of other women ophthalmologists. During the past year, and all throughout her career, she has used her leadership roles to promote and support women. This effort will have a lasting impact not only on individual women but also on all women ophthalmologists for years to come. She is also a great mentor to fellows, who find her to be approachable and always willing to share her wisdom.

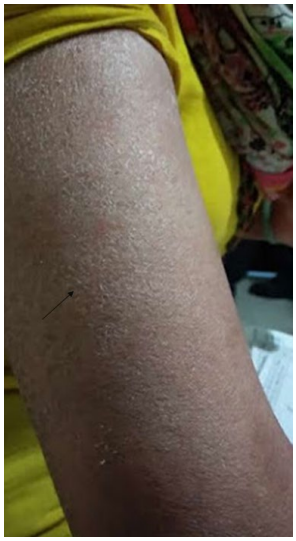
Dr. Kim

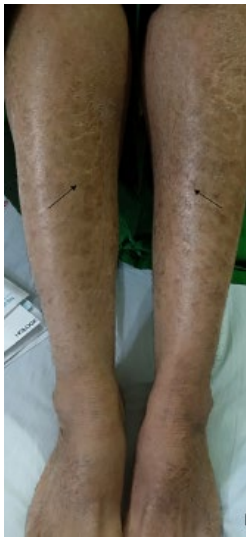
MYSTERY IMAGE

BLINK









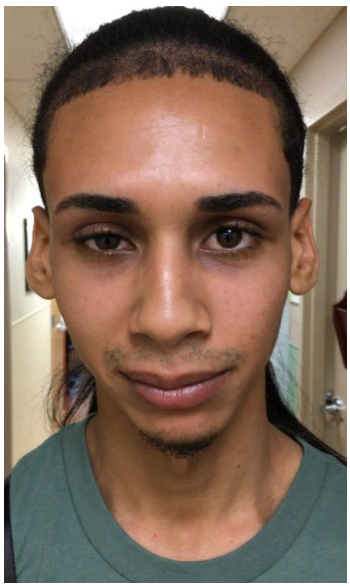
WHAT IS THIS MONTH'S MYSTERY CONDITION?
Visit aao.org/eyenet to make your diagnosis in the comments.

LAST MONTH'S BLINK

Marin-Amat Syndrome

A 20-year-old man complained of involuntary closure of his right eye when he smiled. He had been diagnosed with and treated for right-side Bell palsy about a year ago, with nearly complete resolution of his symptoms. Examination revealed closure of both the upper and lower right eyelids upon smiling. The ocular exam was otherwise normal, and his visual acuity was 20/20 in both eyes.

Synkinesis is described as involuntary muscle movements that are triggered by voluntary muscle movements. Marin-Amat syndrome specifically refers to a rare form of facial synkinesis in which the orbicularis oculi muscle is activated with the voluntary movement of the lower facial muscles (e.g., smiling).[1] It is thought to be caused by aberrant seventh nerve regeneration after trauma or as a result of Bell palsy. In this patient, the decision was made to monitor the symptoms closely and to consider botulinum toxin injections in the future.



WRITTEN BY **SUMANA S. KOMMANA, MD,** AND **UPNEET K. BAINS, MD,** TEMPLE UNIVERSITY HOSPITAL, PHILADELPHIA. PHOTO BY **SUMANA S. KOMMANA, MD.**

EXTRA **MORE ONLINE.** For an eight-second video of the patient's synkinesis, see this article at aao.org/eyenet.

1 Jethani J. *Indian J Ophthalmol.* 2007;55(5):402-403.

LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

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

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted. and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

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

8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

LUCENTIS®
[ranibizumab injection]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

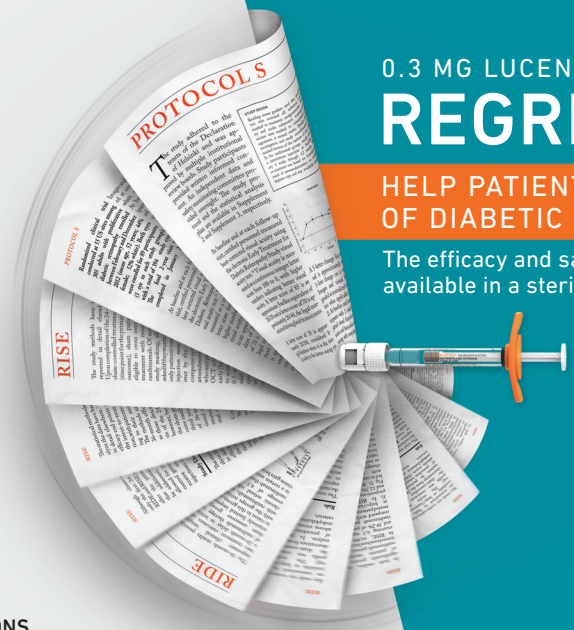
Initial US Approval: June 2006
Revision Date: LUC/021815/0050(4) 2017

0.3 MG LUCENTIS PREFILLED SYRINGE

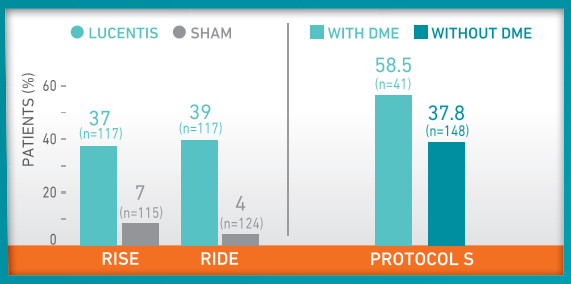
REGRESSION DELIVERED[1]

HELP PATIENTS TURN BACK TO AN EARLIER STAGE OF DIABETIC RETINOPATHY (DR)[1]

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a sterile glass prefilled syringe.[1]



≥2-STEP IMPROVEMENTS AT 2 YEARS[1]*



≥3-STEP IMPROVEMENTS AT 2 YEARS[1]:

RISE AND RIDE
- LUCENTIS 0.3 mg: 9% (n=117) and 17% (n=117), respectively
- Sham arms: 0% (n=115) and 2% (n=124), respectively

PROTOCOL S
- Patients without DME: 28.4% (n=148)
- Patients with DME: 31.7% (n=41)

Confidence intervals (95%): ≥2-step—RISE: 31% (21%, 40%); RIDE: 35% (26%, 44%). Protocol S (DR with DME): 58.5% (43.5%, 73.6%); (DR without DME): 37.8% (30%, 45.7%). ≥3-step—RISE: 9% (4%, 14%); RIDE: 15% (7%, 22%). Protocol S (DR with DME): 31.7% (17.5%, 46%); (DR without DME): 28.4% (21.1%, 35.6%).[1]

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
- Diabetic retinopathy (DR)
- Diabetic macular edema (DME)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time

Please see Brief Summary of LUCENTIS full Prescribing Information on following page.

*The following clinical trials were conducted for the **DR & DME** indications: ***RISE & RIDE***—Two methodologically identical, randomized, double-masked, sham injection–controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. ***Protocol S***—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.[2-3]

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).[1]

DME, diabetic macular edema.

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **2.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **3.** Gross JG, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314:2137-2146.

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LUCENTIS®
RANIBIZUMAB INJECTION