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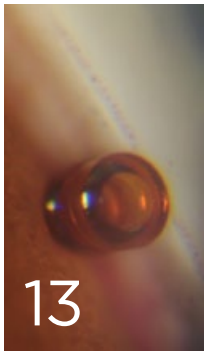
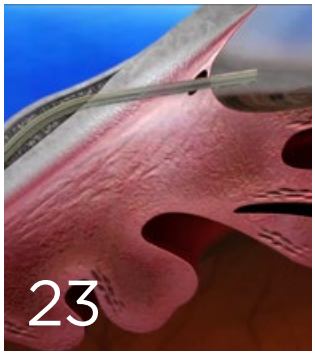
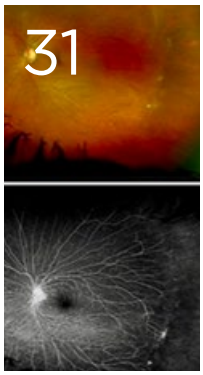
VOLUME 23 • NUMBER 11







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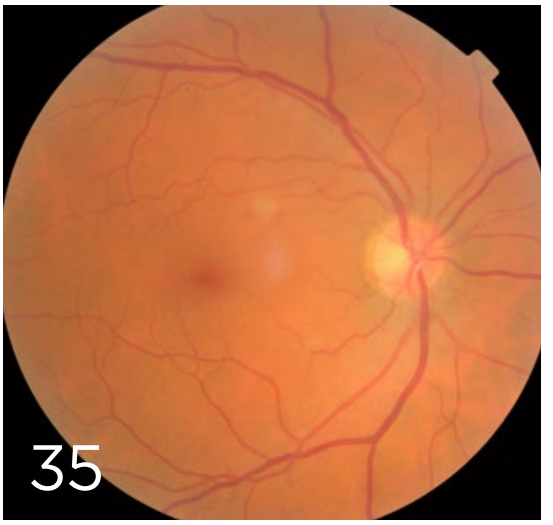
EyeNet*® *Magazine (ISSN 1097-2986) is published monthly by the American Academy of Ophthalmology, 655 Beach St., San Francisco, CA 94109-1336, as a membership service. Subscription is included in U.S. members' annual dues. International Member, IMIT, $135 per year. Nonmember in U.S., $150 per year. Nonmember outside U.S., $210 per year. Periodicals Postage Paid at San Francisco, CA, and at additional mailing offices. POSTMASTER: Send address changes to *EyeNet*, P.O. Box 7424, San Francisco, CA 94120-7424.



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Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

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The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and increase in tears (1%-10% of patients).

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and full Prescribing Information on Oxervate.com/HCP.

*Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment. Based on results from the REPARO trial (Europe, NGF0212; N=156) and the US trial (NGF0214; N=48).[7,8]

References: 1. OXERVATE (cenegermin-bkbj) full prescribing information. Dompé. May 2019. **2.** FDA approves first drug for neurotrophic keratitis, a rare eye disease [FDA news release]. August 22, 2018. **3.** Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. **4.** Voelker R. New drug treats rare, debilitating neurotrophic keratitis. *JAMA*. 2018;320:1309. **5.** Müller LJ, Marfurt CF, Kruse F, Tervo TMT. Corneal nerves: structure, contents and function. *Exp Eye Res*. 2003;76:521-542. **6.** Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579. **7.** Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology*. 2018;125:1332-1343. **8.** Center for Drug Evaluation and Research, US Food and Drug Administration. Oxervate (cenegermin-bkbj) BLA 761094. Medical Review(s). July 19, 2018. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761094Orig1s000TOC.cfm.

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Brief Summary of Safety

Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

ADVERSE REACTIONS

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

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [*see Clinical Studies (14)*].

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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Opinion

RUTH D. WILLIAMS, MD

#ThisIsMyLane

Here's an interesting question: Should the Academy—whose mission is protecting sight and empowering lives—take a position on gun violence?

I grew up in Wyoming, where children learn gun safety by the time they can read. I got my first permit for hunting antelope when I was in 7th grade; by the time I could drive a car, I'd learned to track an elk. I drove a pickup truck with a full gun rack, and there was a pistol in the glove box. But none of this prepared me for the realities of gun violence. During my first night on call as an ophthalmology resident, my first patient was a 13-year-old girl who had been shot by her boyfriend. The bullet severed her left optic nerve. I treated many more victims of gun-related eye injuries during my rotations at Highland Hospital, Alameda County's public hospital in Oakland, California. Every time, the experience was jarring, tragic, and memorable.

At the September meeting of the Academy Board of Trustees, Academy President George Williams, MD, asked, "How many of you have cared for patients with gun-related eye injuries?" It looked like every hand in the room was raised. He then asked, "How many of you have *never* cared for a patient with a gun-related eye injury?" Only one person responded: Donald Tan, MD, a cornea specialist from Singapore who is one of two international trustees. Every American ophthalmologist in the room was experienced in handling ocular trauma caused by gun violence—and our only attending board member from another country had never seen a case.

Seven major U.S. medical organizations have developed recommendations to address firearm-related injury and death and have published a paper in the *Annals of Internal Medicine*.[1] The coalition is emphasizing a public health approach that mirrors the strategies to decrease the harmful effects of tobacco use, motor vehicle accidents, and unintentional poisoning. Their recommendations include background checks for firearm purchase, extreme risk protection orders (temporary removal of firearms from those at imminent risk of gun violence), and protection against "gag" laws, which prevent physicians from counseling at-risk patients about the dangers of guns in the home. The paper supports education about safe storage of firearms and cautions about lumping gun violence with mental illness. Finally, the coalition urges policymakers to address ". . . firearms with features designed to increase their rapid and extended killing capacity."

As the authors point out, developing effective strategies to decrease gun-related injury and death requires good research—and there isn't much. For instance, in ophthalmology, there are many papers about eye injuries in children from air and pellet guns, but very few that address visual outcomes following gun trauma. Furthermore, we need research into factors that lead to gun violence. And the strategies to prevent it must be evidence-based. Private and public funding is needed to provide the epidemiologic data around gun-related injuries and the effectiveness of prevention tactics.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Of course, some ophthalmologists (and most Wyomingites) want to protect gun ownership. But tackling gun violence as a public health issue doesn't necessarily infringe on this right. In fact, the authors of the *Annals* paper note, "While we recognize the significant political and philosophical differences about firearm ownership and regulation in the United States, we are committed to reaching out to bridge these differences to improve the health and safety of our patients, their families, and communities, while respecting the U.S. Constitution."

The Academy Board of Trustees voted unanimously to endorse the paper, support its recommendations, and join the coalition of medical organizations who are calling for policies to help decrease firearm injuries and death in the United States. So, to refer back to my opening question, the answer is yes: The Academy regards the tragedies of gun violence as a public health issue. It is our responsibility as physicians to help prevent gun-related eye injuries.

1 McLean RM et al. *Ann Intern Med.* Published online Aug. 7, 2019.

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GLAUCOMA

CyPass Update: IOP Effect Seen, Cell Loss Noted

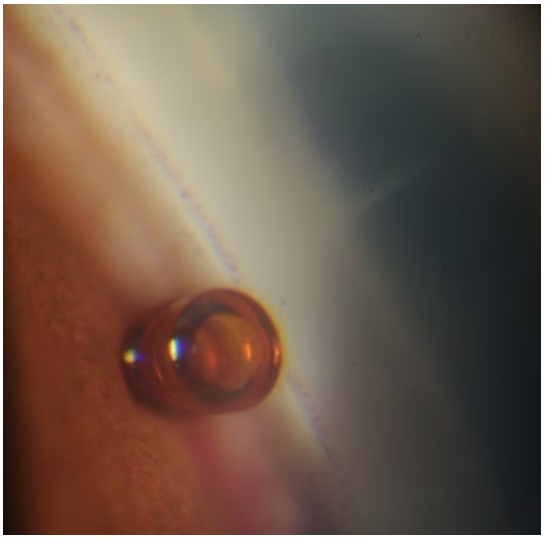
FIVE YEARS OF PATIENT FOLLOW-UP has confirmed that late endothelial cell loss occurs in mild to moderate open-angle glaucoma (OAG) patients implanted with the CyPass supraciliary microstent, combined with cataract surgery. But the remaining cells continued to keep the corneas clear, and the microstent reduced intraocular pressure (IOP) throughout the study.[1,2]

Alcon withdrew the CyPass from the market in August 2018, and the FDA later issued a class 1 recall. These steps were triggered by earlier monitoring results, which suggested that CyPass-treated eyes had accelerated cell loss at four and five years after surgery.

Recent findings. COMPASS XT investigators reported a mean decrease in endothelial cell density (ECD) of 20.4% in the CyPass eyes at five years after the combined surgery, compared to a mean 10.1% drop in the phacoemulsification-only control eyes.

This contrasted with the results at two years, when there was no difference in mean ECD between the two groups, said Jonathan H. Lass, MD, at Case Western Reserve University and University Hospitals Eye Institute in Cleveland.

"This is going to alert cornea and glaucoma specialists to be looking more closely at these patients over the long term. And then if they see signs of endothelial cell loss, such as the development of localized or diffuse striae and/or corneal edema, to do specular microscopy to evaluate the eyes further," Dr. Lass said. "I would also refer clinicians to the ASCRS consensus statement regarding management."[3]



George R. Reiss, MD

IN PLACE. *A well-positioned CyPass in the supraciliary space with distal opening in front of the trabecular meshwork.*

Other five-year outcomes with the CyPass device were positive, said principal investigator George R. Reiss, MD, at Eye Physicians and Surgeons of Arizona, in Glendale and Scottsdale. The device was "well tolerated in the majority of patients," he noted. "As compared with phacoemulsification alone, the group with CyPass had better pressure reduction and was more likely to be off medications."

At five years, the mean reduction in IOP was slightly greater in the microstent cohort (8.4 mm Hg; 95% confidence interval [CI]: 7.8-8.9) than in the control group (8.0 mm Hg; 95% CI: 6.8-9.2), the investigators reported. (However, the study was not powered sufficiently to evaluate effectiveness with statistical significance.)

Adverse events were few, and there were no serious device-related adverse events. Three of the eyes had transient focal corneal edema in the region of the microstent at 33, 55, and 60 months, but no persistent corneal edema occurred in any eyes, the researchers reported.

Innate resilience? Previous studies of other causes of endothelial damage have shown that the endothelium is resilient, and this possibly explains why the corneas of patients who had received the CyPass remained healthy despite localized cell loss, Dr. Lass said.

"The issue is not the absolute endothelial cell density so much as it is the rapidity of the damage occurring. Because, even at low cell counts, the remaining cells—if given the chance—have the ability to adapt," Dr. Lass said. "They get larger, change shape and size, increase the number of pump sites on their lateral margin, and migrate over to mitigate the damage. That's probably what's happening here, but further studies are needed."

Looking ahead. CyPass was originally approved for mild to moderate glaucoma, but it might be more appropriate for use in more severe glaucoma cases in which surgical IOP reduction without bleb formation is desired, the COMPASS XT investigators suggested.

"Hopefully the device will make its way back into the market," Dr. Reiss

said. "Many glaucoma specialists miss this supraciliary stenting option."

—Linda Roach

1 Reiss G et al. *Am J Ophthalmol.* Published online Aug. 1, 2019.
2 Lass JH et al. *Am J Ophthalmol.* Published online Aug. 1, 2019.
3 Rhee D et al. Preliminary ASCRS CyPass Withdrawal Consensus Statement. https://ascrs.org/CyPass_Statement. Accessed on Sept. 18, 2019.
Relevant financial disclosures—Dr. Lass: Alcon: S; Transcend Medical: S. Dr. Reiss: Aerie: L; Alcon: C,L,S; Allergan: C,S; Bausch Medical: L; Glaukos: L; Santen/InnFocus: C,S.

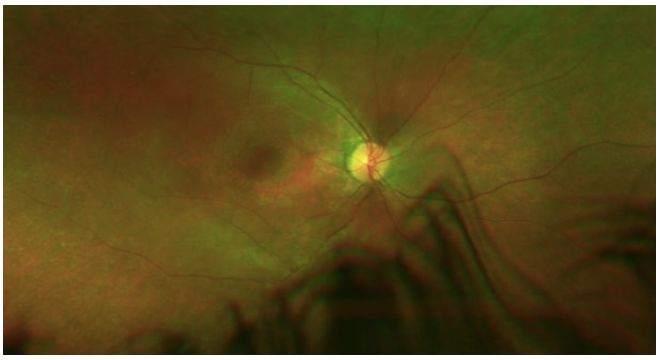
PEDIATRICS

Genetic Dx in Kids: Knowledge Needed

MANY EARLY-ONSET OCULAR DIS-orders are genetic, yet pediatric ophthalmologists lack a solid understanding of genetic disorders and how to approach them, according to a survey conducted by the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) Genetic Eye Disease Task Force.[1]

"No one can know everything," conceded task force chair Arlene V. Drack, MD, at the University of Iowa in Iowa City. "But pediatric ophthalmologists should be able to recognize a disorder as potentially genetic and either pursue a workup or refer to the appropriate subspecialist."

The 16-question survey, which was emailed to 1,489 AAPOS members, focused on physicians' ability to understand and use genetic tests and to counsel patients. While most respondents (93%) reported caring for children with genetic eye disorders on a weekly basis, nearly half (48%) reported no understanding of genetic testing modalities. A majority (81%) described themselves as "a little or not at all comfortable" explaining genetic test results



EARLY DX. *Nystagmus in an infant, along with visual loss, should raise suspicion for Leber congenital amaurosis (shown here). An FDA-approved therapy is now available for selected cases.*

NEURO-OPHTHALMOLOGY

Visual Signs May Herald Parkinson Disease

MAYO CLINIC RESEARCHERS HAVE FOUND THAT visual abnormalities are among the most frequent nonmotor symptoms in the early stages of Parkinson disease (PD).[1] In some cases, visual symptoms could indicate PD onset before more specific physical signs and symptoms develop. They may even predict disease progression.

"Parkinson can affect almost any part of the visual system, including subtle changes in the retina, ocular motor function, and cortical visual processing," said John J. Chen, MD, PhD, at the Mayo Clinic in Rochester, Minnesota.

The early signs. In a literature review, Dr. Chen and his colleagues described the ophthalmic abnormalities that can be seen in PD and outlined how dopaminergic therapy can influence these symptoms. For instance, they noted that impairments in color vision and contrast sensitivity in PD patients may be related to the loss of dopaminergic neurons in the retina.

"These visual manifestations are important to recognize because some of them will be symptomatic in our patients, while others may end up being a prodromal symptom that can help with the PD diagnosis," Dr. Chen said.

Prodromal clues? The prodromal visual manifestations of PD are "the most exciting part of the study," he said. "Some of these may precede the development of PD and could possibly be used as a biomarker to predict or follow progression."

To that end, Dr. Chen is conducting a pilot study to explore the use of optical coherence tomography in patients with REM (rapid eye movement) sleep behavior disorder, which is strongly associated with a risk for conversion to PD.[2]

Clinical implications. Most ophthalmologists know that patients with PD often have dry eye from poor blink rate and may also have some ocular motility abnormalities, Dr. Chen said. But PD can cause other visual abnormalities that often go unrecognized—not only impaired color vision and contrast sensitivity but also problems with stereopsis, saccades, and smooth pursuit eye movements. Patients may even develop visual hallucinations.

"These are important to identify," Dr. Chen said, "because these symptoms can be explained to the patient" as part of the disease process. Moreover, he said, "they may even lead to a diagnosis of unrecognized PD" in some cases.

—Miriam Karmel

1 Turcano P et al. *J Neurol.* 2019;266(9):2103-2111.
2 Postuma RB, Berg D. *Nat Rev Neurol.* 2016; 12(11):622-634.
Relevant financial disclosures—Dr. Chen: None.

to patients. Of those who order testing, 90% work with a genetic counselor.

The good news: Most respondents appeared eager to learn more about testing modalities, citing interest in continuing education.

Missed diagnoses? Despite two email reminders, the survey response rate was only 18%. The researchers suspect that the nonresponders may think they don't see patients with genetic disorders, so a survey about genetic eye disease does not apply to them. But, said cochair Virginia Miraldi Utz, MD, at the University of Cincinnati, "most likely, they are seeing at least one genetic eye disease patient a week, but they may not realize that the underlying cause of that patient's problem is genetic."

What you don't know . . . Most pediatric ophthalmologists have not been trained to do genetic testing for congenital/infantile nystagmus, infantile/juvenile cataracts, pediatric glaucoma, and congenital malformations. And this is occurring at a time when novel gene-based diagnostic strategies[2] and therapies continue to emerge.

"It is not common for children to have serious eye disorders," Dr. Drack said. Thus, when such disorders present, she urged ophthalmologists to have a high level of suspicion for a genetic cause. "We won't find what we don't look for." —*Miriam Karmel*

1 Drack AV et al. *J AAPOS.* Published online June 21, 2019.

2 Gillespie RL et al. *Ophthalmology.* 2016;123(1): 217-220.

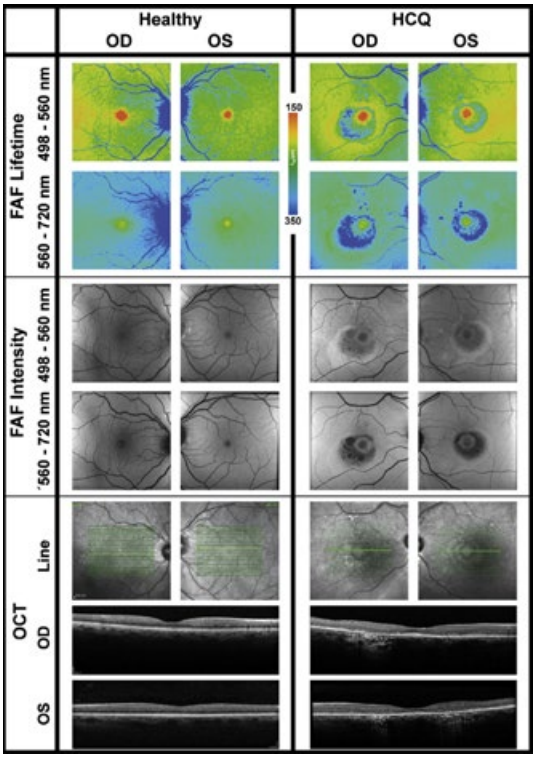
Relevant financial disclosures—Drs. Drack and Utz: None.

RETINA

FLIO May Help in Screening for HCQ Toxicity

CAN A NOVEL IMAGING TECHNOLOGY reveal retinal damage earlier than currently available imaging modalities? Researchers have yet to prove that it can, but they are pursuing leads that fluorescence lifetime imaging ophthalmoscopy (FLIO) may be useful for detection of hydroxychloroquine (HCQ; Plaquenil) toxicity in a retina that appears otherwise healthy.[1]

"FLIO is a novel technology that is not yet widely known, but it has already revealed disease-related patterns for age-related macular degeneration and other retinal conditions," said Lydia Sauer, MD, at the John A. Moran Eye Center in Salt Lake City, Utah. "We believe that it has great potential to enhance the diagnosis of retinal diseases by detecting metabolic changes in the retina, before overt damage occurs." Other imaging modalities, including optical coherence tomography (OCT), describe changes only after retinal damage is manifest.



COMPARISON. *Fundus autofluorescence lifetime and intensity images, as well as OCT imaging, from a healthy subject and a patient with severe HCQ toxicity.*

What FLIO may tell us. This noninvasive imaging technology measures the span of time that naturally occurring retinal fluorophores glow, following excitation with a laser pulse. This is known as the autofluorescence lifetime.

Dr. Sauer and her colleagues harnessed FLIO to measure retinal toxicity from HCQ, which is well-known for its ability to cause retinal damage.

Study specifics. The researchers used a modified Spectralis OCT (Heidelberg Engineering) to measure fluorescence lifetimes in 58 patients. Of these, 12 had definite HCQ toxicity; eight were clinically normal and considered at low risk, as they had been on HCQ for less than five years; 16 were clinically normal but considered high risk, as they had been on the drug for more than five years; and 22 were age-matched healthy controls.

All of the patients with definite HCQ toxicity showed significantly prolonged FLIO lifetimes in regions of damage. Of the clinically normal patients, nine of the 16 in the high-risk HCQ group (56%) and two of the eight in the low-risk group (25%) showed prolonged autofluorescence lifetimes in a pattern suspicious for HCQ toxicity. No such patterns were observed in the healthy controls.

Next steps. Dr. Sauer stressed that researchers are unsure about the metabolic and structural origins of the altered FLIO lifetimes. Thus, they plan to monitor their cohort of "suspicious" patients to determine whether FLIO findings suggestive of HCQ toxicity evolve to overt damage visible with established imaging modalities, she said. "This would prove our hypothesis and may allow us to change individual treatments based on FLIO findings to preserve eyesight." —*Miriam Karmel*

1 Sauer L et al. *Ophthalmol Retina.* Published online May 2, 2019.

Relevant financial disclosures—Dr. Sauer: Novartis: C; Tesseract: C. Heidelberg Engineering provided nonfinancial support.

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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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Anti-VEGF for ROP: Impact on Developmental Outcomes for the Eye and Brain

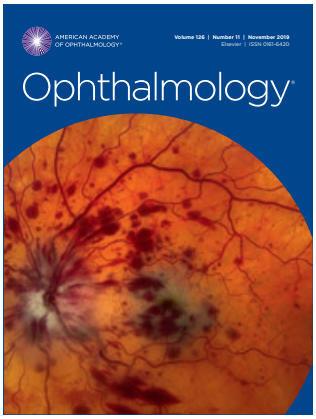
November 2019

Fan et al. looked at ocular and neurodevelopment outcomes for toddlers born prematurely who had received intravitreal injections of bevacizumab for type 1 retinopathy of prematurity (ROP). Their findings support the growing trend of using anti-VEGF drugs to manage ROP.

This prospective case-controlled study was conducted from June 2014 to January 2019 at Chang Gung Memorial Hospital in Taiwan. The final analysis set included 148 patients (85 boys, 63 girls), grouped as follows: premature infants without ROP (group 0; n = 79), premature infants with ROP whose condition regressed spontaneously without treatment (group 1; n = 31), and premature infants with ROP who were treated with a single intravitreal injection of bevacizumab (group 2; n = 38).

Patients in all three groups received follow-up, and their ocular developmental and neurodevelopmental outcomes were compared when they were 1 to 3 years old. Ocular evaluation included cycloplegic refractometry, axial length, and Cardiff acuity. Neurodevelopment was assessed with the Bayley Scales of Infant and Toddler Development (third edition).

The mean age at evaluation was 1.49 years. As expected, gestational age (GA), birth weight, and Apgar scores were significantly higher in group 0. There were no significant differences between groups 1 and 2 in demographics or systemic risk factors, except for younger GA in group 2. Cylindrical power was significantly larger in groups 1 and 2 compared with group 0. Relative to group 0, the spherical equivalent in group 2 was significantly more myopic, and Cardiff acuity was much poorer. Groups 1 and 2 were comparable in refractive status, axial length, and Cardiff acuity.



There were no meaningful differences in neurodevelopment between any of the three groups (after adjusting for GA and systemic risk factors), including the risk of poor neurodevelopmental outcomes.

The researchers noted that two previous retrospective studies raised concerns about neurodevelopmental outcomes for infants with ROP treated with bevacizumab. Although this study demonstrated no such disadvantage, the authors acknowledged that their sample size may have been inadequate for detecting small but clinically significant differences. *(Also see related commentary by Susan M. Carden, MBBS, PhD, in the same issue.)*

Cataract Surgery, Surgeon Volume, and VA Results

November 2019

The association between higher cataract surgery volume and lower complication rates is well recognized. However, data are limited on the relationship between case volume and visual outcomes. **Cox et al.** aimed to build on existing evidence by exploring potential correlations. Using a large database, they found that the work of higher-volume cataract surgeons performing phacoemulsification resulted in slightly improved visual acuity (VA) outcomes and lower complication rates.

For this study, the researchers included 35,880 eyes that received small-incision cataract surgery (SICS) or phacoemulsification with intended IOL placement. All surgeries were performed in 2015 at the Aravind Eye Hospital in Madurai, India. Bivariate linear regression with random effects was used to assess each eye's uncorrected VA (UCVA) at follow-up relative to surgeon case volume and to other demographic and case factors. Factors with a p value below 0.20 on bivariate regression were included in random-effects multivariate regression modeling. The primary objective was to assess relationships between surgeon case volume and patients' visual outcomes after cataract surgery. Secondary objectives included exploring potential correlations between other case characteristics

and VA outcomes and between case volume and complication rates.

The operations were performed by 69 surgeons; individual case volume for 2015 ranged from 76 to 2,900. In general, higher case volume was independently associated with a statistically significant (but clinically modest) improvement in UCVA after phacoemulsification but not after SICS. However, this effect appeared to plateau at a caseload of approximately 350 cases per year. The favorable UCVA trend was not observed for surgeons who performed between 1,501 and 2,000 cases per year; their patients' visual outcomes were worse than for other surgeon groups, except the lowest-volume cohorts. Higher case volume was associated with significantly lower complication rates with phacoemulsification as well as with SICS. Younger patient age was independently linked to better visual outcomes and lower complication rates with both procedures.

Greater surgeon experience correlated with lower complication rates for phacoemulsification but not for SICS. Level of experience did not correlate with VA outcomes.

The findings may help to inform the design and workflow of ophthalmology clinics, said the authors. This might have particular relevance in countries with a large burden of cataract-related visual impairment and a high patient-to-surgeon ratio. *(Also see related commentary by Robert J. Campbell, MD, MSc, in the same issue.)*

Outcomes of Nd:YAG Laser for Floaters

November 2019

Vitreous floaters can be addressed with the Nd:YAG laser, but research with objective structural and functional outcomes is lacking. **Nguyen et al.** conducted a retrospective comparative study of eyes with floaters and found that those treated with the Nd:YAG laser had reduced vitreous density but similar visual function as those that were untreated. Because the vision of some treated eyes was superior to that of untreated eyes, a prospective randomized study with uniform laser treatment parameters would be helpful, the authors said.

The study included 132 eyes (132 subjects; mean age, 56 years); 97 had vitreous floaters and 35 were unaffected. Of the 97 with floaters, 38 previously received Nd:YAG laser treatment; the other 59 had been evaluated but not treated and served as controls. Of the 38 treated patients, 25 were unhappy with their result and were seeking vitrectomy; the remaining 13 were satisfied with their result and remained under observation only. These two groups were comparable in age and visual acuity.

Visual acuity (VA) was measured with standard Snellen charts, and contrast sensitivity function (CSF) was assessed with the Freiburg Acuity Contrast Test. Statistical analyses included the Fisher's exact test to compare prevalence of pseudophakia, posterior vitreous detachment, and myopia. Multivariable linear regression was used to explore differences between the study groups, after adjusting for confounders.

Compared to untreated patients with floaters, patients treated with Nd:YAG laser had a 23% reduction in vitreous echodensity—but had comparable well-being, VA, and CSF.

The objective measures of CSF testing and quantitative ultrasonography yielded no differences in well-being or VA between Nd:YAG-treated patients and untreated controls.

However, these tests did show improvement in echodensity that was unrelated to well-being. The authors noted that this difference may relate to selection bias, because most patients who presented were unhappy with their Nd:YAG outcome.

The results indicate that many patients who receive Nd:YAG therapy for floaters remain symptomatic and seek further treatment. The authors suggest that future studies explore whether certain types of floaters are more responsive than others to laser treatment. They favor prospective randomized studies, with uniform protocols, focused on quantitative measures of quality of life and objective assessment of structural outcomes.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

U.K. Report: Resource Use for Geographic Atrophy

November 2019

Chakravarthy et al. used a large clinical dataset to estimate the use of eye care resources among patients with geographic atrophy (GA). They found that resource use is highest among those with GA in one eye and choroidal neovascularization (CNV) in the other.

For this retrospective analysis, the researchers collected data from 10 National Health Service clinical sites in the United Kingdom on patients with GA or early/intermediate age-related macular degeneration (AMD). Patients were seen between October 2000 and February 2016.

Patients were sorted into four subgroups: 1) Those with GA in both eyes (GA:GA), 2) those with GA in one eye and CNV in the fellow eye (GA:CNV), 3) those with GA in one eye and AMD in the fellow eye (GA:AMD), and 4) those with AMD in both eyes (AMD:AMD). Primary outcomes were the median number of visits that took place during the first two years after diagnosis of GA or AMD and the cost of clinical tests performed during these visits.

The researchers evaluated data on 7,159 patients. Results were as follows:

- Those in the AMD:AMD subgroup (n = 6,079) had a median of 2 visits and a cost of £184 during the two-year period following diagnosis.
- Patients in the GA:GA subgroup (n = 442) had a median of 3 visits and a cost of £277.
- Patients in the GA:AMD subgroup (n = 283) had a median of 4 visits and a cost of £369.
- Those in the GA:CNV subgroup (n = 355) had a median of 15 visits and a cost of £1,581.

With regard to clinical monitoring, the authors noted variations among testing strategies. For instance, while patients in the GA:CNV subgroup were commonly evaluated via optical coherence tomography, those in the other subgroups were not.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Retinal Changes That Precede DR in Type 1 Diabetes

November 2019

Few studies have focused on the initial retinal changes in children who have type 1 diabetes without diabetic retinopathy (DR). **Inanc et al.** sought to determine whether the abnormal glucose metabolism that occurs in type 1 disease affects the microcirculation of children with the disease. They compared their findings with those for healthy children and noted that diabetic eyes without clinically detectable DR had alterations in the acircularity index (AI), perimeter, and foveal density of parafoveal capillaries in the deep capillary plexus, which preceded enlargement of the foveal avascular zone (FAZ). These parameters might serve as imaging biomarkers to define early DR, the researchers said.

This cross-sectional prospective study included 60 patients with well-controlled diabetes and clinically undetectable DR as well as 57 age-matched controls. Optical coherence tomography angiography (OCTA) was performed, and various parameters were measured, including FAZ area, nonflow area, superficial and deep vessel density, FAZ perimeter, FAZ AI, and foveal density in the 300 µm (FD-300) surrounding the FAZ. The authors looked at the findings for these parameters in relation to the duration of diabetes and the level of glycated hemoglobin (HbA_{1c}).

Differences in mean values between the patients and control children were significant for FAZ perimeter ($p < .001$), AI ($p = .001$), and FD-300 ($p = .009$). Significant differences between these groups also were noted for vessel density in the deep superior hemiparafovea, deep temporal parafovea, and deep superior parafoveal zones ($p = .008$, $p = .015$, and $p = .005$, respectively). There were no meaningful correlations between OCTA findings and disease duration or HbA_{1c} levels.

These findings imply that defects in retinal microcirculation and irregularities at the FAZ margin can occur before DR becomes clinically apparent. The observed changes in FD-300, AI, FAZ perimeter, and vessel density of the parafoveal capillaries in the deep capillary plexus precede enlargement of the FAZ. The authors recommend further investigation of the role of OCTA in disease detection and treatment guidance for children with type 1 diabetes.

Vismodegib for Basal Cell Carcinoma

November 2019

Basal cell carcinoma (BCC), the most common skin cancer, accounts for 90% of malignant tumors of the eyelid. **Eiger-Moscovich et al.** looked at the effectiveness of vismodegib, a Hedgehog pathway inhibitor, for treating orbital and advanced periocular BCC. They found that treatment according to an individualized maximally tolerated dose achieved responses similar to those achieved in the pivotal ERIVANCE study. The authors emphasized that longer-term studies are needed to gauge prognosis.

This retrospective series included 21 patients (median age, 76 years; 16 men) with biopsy-proven periocular BCC (n = 6) or orbital BCC (n = 15). In most cases, treatment was given for five to seven months, at the usual dosage of 150 mg per day, followed by an intermission. If deterioration was observed, treatment was resumed. The aim was to customize each patient's treatment to the maximally tolerated dose. Some patients received a partial dose to minimize adverse events such as hepatotoxicity.

The median duration of vismodegib treatment was nine months. The median follow-up period was 17 months after treatment cessation. The clinical response was complete in 10 patients, partial in 10 others, and stable in one patient. No patient had progressive disease (defined as an increase in tumor size of >20%). Among the complete responders, two were still being treated and eight had finished treatment at the time of this report. Five of the eight maintained their complete response by 16 months; the other three had recurrence within eight months.

Treatment response did not seem affected by orbital involvement or tumor stage. Nearly all treatment-related adverse reactions were low grade; the most common were muscle spasm (76%) and dysgeusia (57%). The only grade 3/4 adverse event was hepatotoxicity (10%). Eight patients discontinued treatment due to side effects. Five patients died, most from reasons that appeared unrelated to vismodegib. However, one death (from sepsis) may have been related to treatment.

To the authors' knowledge, this is the largest study of vismodegib therapy for locally advanced periocular BCC. Response rates to maximally tolerated doses were comparable to those with the ERIVANCE protocol, yet the optimal treatment protocol remains unknown, and longer studies are needed.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Driving at Night: Do Yellow-Tinted Lenses Improve Vision?

October 2019

Advertising claims for yellow-tinted lenses state that they improve night vision by reducing glare and eyestrain. But in a study that involved simulating nighttime driving conditions, **Hwang et al.** found that donning the lenses did not improve participants' ability to detect pedestrians. The findings indicate that yellow lenses do not live up to product claims and that more work is needed to address nighttime driving challenges such as headlight glare (HLG).

For this single-center cohort study, the researchers enrolled 22 adults, all of whom had normal visual acuity. For the main experiment, 12 participants (mean age, 28 years) were assessed under nighttime conditions for their ability to see and respond to a pedestrian wearing a dark navy-blue shirt. The remaining 10 participants were evaluated for their ability to detect and respond to a pedestrian wearing an

orange shirt—and these 10 were divided into two groups, one of younger (n = 6; mean age, 27 years) and another of older (n = 4; mean age, 70 years) participants.

The researchers developed a simulator that replicates the HLG from oncoming cars. Each participant "drove" scripted night-driving scenarios four times (once with each of the three commercially available glasses with yellow lenses and once with clear glasses); the HLG simulator was turned on or off for each scenario. Before starting the initial scenario, each participant took at least one introductory drive to become acquainted with the driving simulator environment and the experiment's tasks. The main outcome measure was response time for the critical task of detecting a pedestrian. (The pedestrians were portrayed as either walking alongside the road or attempting to cross the road.)

The researchers found no significant difference in response time with the various yellow lenses for any experimental condition—and no benefit when compared with clear lenses. Among younger drivers, the impact of HLG was more pronounced with the simulation involving the navy-wearing pedestrian. In the simulation involving the orange-wearing pedestrian, older drivers were significantly slower to respond than were younger participants (1.5 seconds vs. 0.3 seconds, respectively).

Thus, yellow lenses did not appear to improve drivers' ability to detect pedestrians at night or to reduce problems with HLG. These findings challenge the notion of recommending the lenses to patients who have poor nighttime vision. *(See also related commentary by Robert W. Massof, PhD, in the same issue.)*

The High Costs of Rx Waste

October 2019

Tauber et al. looked at the effect of unused pharmaceuticals related to phacoemulsification surgery and found the financial and environmental burdens to be high, particularly for discarded eyedrops.

For this descriptive qualitative study, the authors included four surgical sites in the northeastern United States: a private ambulatory care center, a private tertiary care center, a federally run medical center for veterans, and a private outpatient facility. Pricing and other data for use of services and pharmaceuticals were obtained for each facility. The volume or weight of medications remaining after routine phacoemulsification procedures (without vitreous loss or other complications) was measured. From these data, the mean costs of medications were calculated per case and per month. Environmental effects were estimated by economic models of input-output lifecycle assessment.

Primary outcomes were the cost of unused pharmaceutical products (in U.S. dollars) and the potential carbon footprint of cataract surgery, as evaluated in the kilogram equivalents of carbon emissions (carbon dioxide [CO_2-e]), air pollution (fine particulate matter emissions of ≤10 μm in diameter [PM_{10}-e]), and eutrophication potential (nitrogen [N-e]).

A total of 116 unique drugs were assessed among the four centers. A cumulative mean 83,070 mL of 183,304 mL per month (45.3%) of pharmaceuticals were unused by weight or volume. (Unmeasured medications were assumed to have no excess left over.)

The annual cost of unused products per site was approximately $195,200. The product type with the greatest amount of waste was eyedrops (65.7% by volume), followed by systemic drugs (59.9%) and injections (24.8%). With regard to pollution, monthly unused products at the ambulatory care center (65.9% by volume), tertiary care center (21.3%), federal medical center (38.5%), and outpatient facility (56.8%) resulted in unnecessary potential emissions of 2,135, 2,498, 418, and 711 kg CO_2-e per month, respectively. Unnecessary potential air pollution among the sites varied from 0.8 to 4.5 kg PM_{10}-e per month, and unnecessary eutrophication potential ranged from 0.07 to 0.42 kg N-e per month.

If these findings can be substantiated and shown to be generalizable in the United States or elsewhere, efforts to reduce such costs may be of value, said the authors. Larger-scale, multicenter studies should be helpful for understanding the full extent and effects of unused pharmaceuticals. Of note in this study: The surgeons and OR staff were not involved in data reporting or analysis, but they were aware of the nature of the study, which may have influenced their use of materials and led to underestimation of the total waste. *(See also related commentary by Paul Lee, MD, JD, in the same issue.)*

GCA and Race: Is There a Correlation?

October 2019

Giant cell arteritis (GCA) is the most common vasculitis in adults and is linked to high rates of morbidity and mortality. Although its incidence in white populations has been studied extensively, little is known about its preponderance in other racial or ethnic groups. **Gruener et al.** explored the racial incidences of biopsy-proven GCA in a tertiary care facility that serves a substantial black population. They observed a similar rate of GCA in black and white patients.

For this study, the authors identified all patients who underwent temporal artery biopsy (TAB) from July 2007 through September 2017 at the Wilmer Eye Institute in Baltimore. Self-reported data on race, sex, and age were tallied and compared with data for all other patients attending the hospital during the same period. Main outcomes were the estimated rates of biopsy-proven GCA among blacks and whites.

Of the 586 patients who underwent TAB (mean age, 70.5 years; 423 [72.2%] women), 167 (28.5%) were black, 382 (65.2%) were white, and 37 (6.3%) were of other or unknown race. Crude annual incidence rates for biopsy-proven GCA were 2.9 per 100,000 blacks and 4.2 per 100,000 whites. Population-adjusted age- and sex-standardized incidence rates were 3.1 and 3.6 per 100,000 black and white patients, respectively (p = .70). The female-to-male incidence ratio was 1.9 (p = .03). The white-to-black incidence ratio was not significant (1.2; p = .66).

Of the 573 individuals ≥50 years

of age, 92 (16.1%) had biopsy-proven GCA. Of these, 14 were black (8.4% of tested black patients) and 75 were white (19.6% of tested white patients). The authors did not consciously apply different clinical criteria or thresholds for offering or performing TAB in the study population; therefore, the higher pretest probability among whites may suggest that the link between symptoms and disease is stronger in this racial group.

Contrary to research suggesting that GCA is more common in whites and that its occurrence in blacks may be almost negligible, this study indicates that blacks and whites have a similar incidence of GCA. Therefore, the authors recommend that the clinical thresholds for diagnosing and managing GCA be the same for white and black populations. *(See also related commentary by Michael K. Yoon, MD, and Joseph F. Rizzo III, MD, in the same issue.)*

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Eye Evaluation Needed in Children With Brain Tumors

JAMA Network Open
Published online August 2, 2019

Visual impairment in children with brain tumors has received limited attention. Ophthalmologic evaluation is not required for most neuro-oncology clinical trials, and visual function is rarely monitored during or after treatment of the tumor. In a study of children with primary brain tumors, **Liu et al.** looked at patterns of referral to ophthalmology and found that more than half of the children were not referred. The authors emphasized that ophthalmologic evaluation of these patients is needed to ensure that visual function deficits are identified and managed.

For this retrospective study, the researchers included 141 children with a primary brain tumor treated at Loma Linda University Children's Hospital and Eye Institute during a five-year period. Outcomes of interest were the incidence of ophthalmic evaluation, the prevalence of abnormal ophthalmic findings, and the association of such findings with tumor characteristics.

The median age of the children was 7 years (range, 0-18 years); 52% were male. Findings showed that 73 patients (52%) did not have any formal ophthalmologic evaluation. The other 68 patients received assessment by one of four pediatric ophthalmologists and/or neuro-ophthalmologists; the total number of eye care visits for these patients was 222.

The mean five-year survival rates for patients with and without eye exams did not differ substantially (78.3% vs. 84.9%, respectively). The median time from tumor diagnosis to initial ophthalmologic evaluation was nine months (range, 0-94 months). Among the 68 examined children, 10 (15%) had visual symptoms at the time of tumor diagnosis, and 61 (90%) had abnormal findings when examined, including strabismus (60%), impaired visual acuity (54%), amblyopia (38%), papilledema (35%), visual field defects (19%), optic atrophy (18%), and keratopathy (15%). Strabismus was more common with posterior fossa tumors. Radiation therapy correlated significantly with amblyopia.

In light of these findings, the authors recommend ophthalmologic referral of children with brain tumors so that visual sequelae can be detected and vision preserved.

Making Telemedicine a Reality

British Journal of Ophthalmology
Published online July 18, 2019

Kern et al. implemented a cloud-based referral platform for medical retina hospital eye services (HES) in the United Kingdom, which was designed to alleviate demands on ophthalmology services by improving communication between opticians and ophthalmologists. In this pilot study, the digital-first program drastically reduced the number of unnecessary referrals, decreased referral wait time, and facilitated communication between health care providers. According to the authors, the platform may serve as a foundation for implementing artificial intelligence.

For their study, the authors initially reviewed records for 103 patients treated at Moorfields Eye Hospital in London. The patients were classified into the HES referral pathway by one of 11 contributing optometrists, who used the cloud-based platform to share data with a single consultant ophthalmologist at Moorfields. The optometrists were instructed to refer all presumable retina cases via the platform. Initial triage was performed by the optometrist, and other types of referrals (e.g., glaucoma, cataract, or anterior segment conditions) were excluded and sent through the conventional general ophthalmic services pathway. The main outcome measure was the reduction of unnecessary referrals.

A review of patient data in a web-based interface showed that 54 (52%) of the 103 patients initially classified into the referral pathway did not need referral to a specialist. Fourteen patients who needed urgent treatment were identified. Usability was measured in duration for data input and review, which averaged 9.2 minutes for optometrists and 3.0 minutes for ophthalmologists. The most common diagnoses were dry age-related macular degeneration (AMD; n = 34), wet AMD (n = 9), epiretinal membranes (n = 7), and choroidal nevi (n = 7).

Data from this and other research suggest that virtual clinic settings are safe for certain ophthalmic conditions. A study of the health economic impact of cloud-based telemedicine services is being planned. Important to the success of such programs is patient satisfaction and acceptability, which should be addressed in future studies, said the authors. *—Summaries by Lynda Seminara*

RESEARCH FUNDING

Research to Prevent Blindness will fund four IRIS Registry research grants in 2020 in a program co-sponsored by the Academy. To find out more about eligibility requirements and how to apply, visit aao.org/iris-registry/data-analysis/research-to-prevent-blindness-research-grants.

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MD Roundtable, Part 2: Selecting the Right MIGS

Microinvasive glaucoma surgeries (MIGS) enable ophthalmic surgeons to perform precise, individualized glaucoma management, but selecting the most appropriate procedure can be difficult. In this second installment of a two-part MD Roundtable discussion, Ahmad Aref, MD, MBA, of the University of Illinois in Chicago, continues the dialogue with Constance O. Okeke, MD, MSCE, of Virginia Eye Consultants in Norfolk, and Albert S. Khouri, MD, of Rutgers New Jersey Medical School in Newark. The experts share thoughts on choosing MIGS modalities in various hypothetical cases.

Controlled Glaucoma With Cataract

Dr. Aref: *Imagine a patient with visually significant cataract and mild to moderate open-angle glaucoma that is controlled to the target intraocular pressure (IOP) with topical medical therapy. You're considering cataract extraction with IOL implantation. Which MIGS would you choose for this?*

Dr. Khouri: The iStent or iStent inject (both Glaukos), or the Kahook Dual Blade (KDB; New World Medical), would be my go-to MIGS for this case. Of course, there are other MIGS that would work for this patient. I have more experience with the iStents and with the KDB, and I've had good results with both.

Dr. Okeke: I agree that the iStent or iStent inject could yield good outcomes for this patient. I tend to prefer the iStent inject because I've found that the results are a bit more efficacious, and the procedure has been fairly easy to learn.

Ab interno canaloplasty (ABiC) and goniotomy are also options for this hypothetical case. For goniotomy, I use either the Trabectome (NeoMedix) or the KDB. In a patient with early-stage controlled glaucoma, my aim would be to get the patient off medication, and I would try to choose a modality with minimal risk of complications. MIGS involve different levels of inflammation and risks of bleeding postoperatively. With goniotomy, there is greater risk of bleeding than with stenting or canaloplasty, in my hands. I probably would choose the iStent inject or ABiC.

I think the Omni surgical system (Sight Sciences), which includes two MIGS mechanisms, canaloplasty and goniotomy, also could work for this patient.

I'm a firm believer that ophthalmic surgeons should get experience with numerous MIGS options. There are often multiple microinvasive procedures that can yield good outcomes, and the reality is that insurance approval in the majority of cases is a deciding factor. The more MIGS modalities you can perform, the better you can tailor care for your patient.

XEN. *Goniotomy, canaloplasty, and the Xen gel stent also are options for a patient with pseudophakia, with the Xen device reserved for advanced disease, according to Dr. Okeke.*

Dr. Aref: For a patient whose glaucoma is controlled with topical agents, would you say that the safety profile is most important, even if there may be some sacrifice in efficacy?

Dr. Okeke: Yes. I wouldn't carry out a procedure if I didn't feel that the efficacy was there because all these MIGS involve risk. Rather, I can achieve similar efficacies with multiple procedures, so I would choose MIGS with the best safety profiles—the ones that will cause the least bleeding and have the lowest risk of inflammation. For me, stenting and canaloplasty tend to be the safest modalities that still are efficacious for mild topically controlled glaucoma.

Uncontrolled Glaucoma

Dr. Aref: *Let's consider the same patient, but now the IOP is slightly above target. Does that change which*

ROUNDTABLE HOSTED BY **AHMAD A. AREF, MD, MBA,** WITH **ALBERT S. KHOURI, MD,** AND **CONSTANCE O. OKEKE, MD, MSCE.**

procedure you'd consider?

Dr. Okeke: For a patient with uncontrolled glaucoma who is on one medication, I would probably choose the iStent inject. I have had better efficacy with the iStent inject than with the first-generation iStent. In one study, the iStent inject yielded an average IOP reduction of 37%, which is substantial.[1]

I also would consider canaloplasty; with this option, my patients have had IOP reductions of approximately 30% to 40%. Canaloplasty can work especially well for a virgin eye (i.e., conjunctiva without prior manipulation) with early glaucoma in which the outflow system is likely to be functional.

> If I'm combining MIGS, I try to tackle an outflow mechanism and an inflow mechanism. [This way] we often can forestall the need for more invasive glaucoma filtering surgery. —*Dr. Aref*

I'm also a big fan of goniotomy. I perform Trabectome most frequently and have good outcomes. However, if I have the option to perform stenting or canaloplasty, which have lower bleeding risk than goniotomy, then I would choose either of those modalities.

Dr. Aref: A major factor I consider when selecting among MIGS is whether the patient is on a systemic anticoagulant. I perform both stenting and goniotomy, but in such a case, I would prefer stenting to avoid the bleeding risk associated with goniotomy.

Dr. Khouri: For a patient with mild to moderate glaucoma and IOP slightly above target, I would still proceed the same way surgically as I would for a patient with controlled pressure. However, I would have a different discussion with the patient preoperatively. Patients must have realistic expectations with MIGS; it's difficult to predict how each case will respond to treatment. For instance, phacoemulsification is an IOP-lowering procedure. When we combine it with stenting or goniotomy, typically we get additional pressure reduction and a reduction in medication burden. Patients with a higher pressure could potentially reach their target IOP with this approach; however, a subset of patients with more refractory disease or uncertain status of the aqueous outflow (and currently we have no means to ascertain Schlemm's and collector channel outflow state) will need additional treatment to reduce IOP further. Each patient must be aware of this possibility.

Primary Versus Secondary

Dr. Aref: *If a patient has secondary open-angle glaucoma—associated with pseudoexfoliation or pigment dispersion—how does that play into your decision-making?*

Dr. Okeke: I tend to perform goniotomy with the Trabectome for my patients who have pseudoexfoliation glaucoma that is too advanced to benefit from selective laser trabeculoplasty (SLT) or have failed to gain adequate control after SLT. In pigment dispersion syndrome, it's a mixed bag. Theoretically, goniotomy is better than stenting to remove the pigment excess, but canaloplasty should also be considered. I've performed goniotomy in several cases of pigment dispersion syndrome, and sometimes I've been surprised that the outcomes weren't better. The pigment can migrate down the outflow channels and cause blockage.

Canaloplasty involves a multidirectional mechanism of opening the Schlemm's canal by teasing apart adhesions and flushing out pigment through the trabecular meshwork pores and on through the outflow system. When I'm already using the iTrack microcatheter (Ellex) for ABiC, or ab interno canaloplasty, I sometimes combine it with a mini–gonioscopy-assisted transluminal trabeculotomy (GATT) to gain additional efficacy with multiple MIGS mechanisms.

Dr. Khouri: Secondary glaucoma is a very broad category that can involve exfoliation or pigmentary glaucoma. I've had excellent results with stenting procedures in steroid-induced glaucoma. I've also had good results with a combination of viscodissection and the iStent or goniotomy. Conversely, I have had patients with uveitic glaucoma who received tube-shunt surgery in one eye, had postoperative complications—hypotony or exposure issues—and then refused to undergo tube-shunt surgery in the fellow eye. For these patients, there still are MIGS options, especially in combination with cataract removal and synechiolysis, which deepens and opens the angle.

It's important to keep in mind that MIGS treatment of secondary glaucoma is not well studied and is off-label. There aren't many evidence-based recommendations yet. Our procedures are based mostly on personal experience, case series, or case reports. I think surgeons should individualize the surgical plan when dealing with secondary glaucoma because we don't yet have the data to support one procedure versus the other.

Dr. Aref: In studies of the Trabectome[2] and the KDB,[3] results of subanalyses often show that the efficacy achieved with these procedures is much higher in patients with pseudoexfoliation glaucoma than in those with primary open-angle glaucoma. I agree that secondary glaucomas are a broad category, but at least for pseudoexfoliation, I think that the evidence is mounting that these goniotomy procedures are highly efficacious.

Uncontrolled Glaucoma Without Cataract

Dr. Aref: *Let's say we have a patient with IOP above the target level but without visually significant cataract. Which MIGS would you consider?*

Dr. Okeke: Several MIGS options could be performed as stand-alone procedures in the absence of cataract extraction. These include goniotomy techniques—the Trabectome, KDB, or GATT—as well as canaloplasty, which can be performed independently with ABiC, or a combination of these techniques, as with the Omni surgical system. The decision to perform canaloplasty versus goniotomy versus a combination would depend on patient characteristics, such as angle anatomy and desired IOP reduction.

Dr. Khouri: The MicroPulse device (Iridex) for transscleral cyclophotoco-

agulation (CPC) is also an option for a stand-alone procedure, regardless of the cataract condition. Another possibility is subconjunctival surgery with the Xen gel stent (Allergan). We generally reserve the Xen device for advanced disease and perform MicroPulse for a range of moderate or more severe glaucoma in which patients want to avoid traditional surgery and the consequent burden of postoperative care and follow-up.

Pseudophakia

Dr. Aref: *If the patient is pseudophakic, do your MIGS options expand at all?*

Dr. Khouri: For pseudophakic patients, the angle is typically more open; you're done with the appositional factor. I find that angle procedures tend to work well in pseudophakic eyes. In contrast, I prefer not to go into the eye to perform intraocular cilioablative techniques, like endoscopic cyclophotocoagulation (ECP), as a stand-alone procedure. The Xen implant is also a good option for patients requiring lower target pressures.

Dr. Okeke: If a patient is pseudophakic, I would go through the gamut of conservative management with laser therapy, using SLT. I would consider MicroPulse if I was concerned about access to the patient's angle and had low concern about post-op inflammation. Goniotomy, canaloplasty, and the Xen gel stent also are options for a patient with pseudophakia, with the Xen device reserved for advanced disease.

Dr. Khouri: MIGS can be effective as stand-alone technologies. In a recent five-year study,[4] investigators evaluated results of treatment with the two first-generation iStents as a stand-alone procedure versus a prostaglandin. The efficacies of the stand-alone stents were similar to those of prostaglandin, with approximately 35% reductions in IOP up to five years.

MIGS do have a role in pseudophakic eyes with uncontrolled IOP, especially when you want to avoid conventional surgery. With more studies like this, it will become easier to make the case for MIGS to patients and to their commercial insurers, who often push back on covering these procedures.

MIGS Combos

Dr. Aref: *Are there any combinations of MIGS that you've found to work exceptionally well?*

Dr. Okeke: I think canaloplasty combines well with goniotomy. The result is flushing the outflow system and removing a portion of the meshwork to help maintain access to those outflow channels. For instance, the Omni system is a device that comprises viscocanaloplasty and goniotomy. In addition, the iTrack combines ABiC with the potential to do a partial goniotomy procedure with a mini-GATT.

Some doctors have discussed combined procedures of, say, a stenting device plus goniotomy. Again, lack of insurance approval can be a limitation for these combined approaches. When we think about combining MIGS that address different mechanisms of action, it's analogous to combining medical therapies. We know that different medications can work synergistically or in an additive way.

We could combine multiple MIGS in the same surgical session, or we can carry out a MIGS-after-MIGS approach in separate sessions. For some cases in which I've used the Trabectome, the result was stable for three or four years and then started to lose efficacy. Because that was a partial goniotomy, I was then able to do ABiC to address the rest of the intact Schlemm's canal and achieve additional IOP reduction. Similarly, in some cases, I've performed stenting first and goniotomy later. By applying MIGS serially, you can extend the time that a patient can be treated in a minimally invasive approach while still getting efficacious pressure lowering.

Dr. Khouri: I rarely combine MIGS. But I would do so, for example, in a patient with multiple comorbidities when the number of OR sessions must be minimized. I don't have a lot of experience with ECP, but I perform MicroPulse CPC often. For patients requiring low pressure who do not want a trabeculectomy or a tube shunt—and if I felt that phacoemulsification and stenting or goniotomy might not be enough—I've added a conservative two-quadrant MicroPulse CPC in the OR. Again, this is based on personal experience, as there is not enough literature on combination MIGS.

Another setting where concomitant sequential OR procedures work would be viscodissection of synechial closure to open the angle and expose the trabecular meshwork, which then would permit angle surgery, especially in uveitic eyes. I think we'll eventually have more evidence-based knowledge about how MIGS devices work together, particularly when the mechanisms of action are complementary, such as a future supraciliary device combined with stenting or goniotomy.

Dr. Aref: My outlook on this is pretty simplistic. If I'm combining MIGS, I try to tackle an outflow mechanism and an inflow mechanism. I do use ECP quite often in my practice. With two-site ECP plus an outflow maneuver—such as with the iStent inject or KDB—in addition to cataract surgery, we often can forestall the need for more invasive glaucoma filtering surgery.

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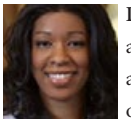

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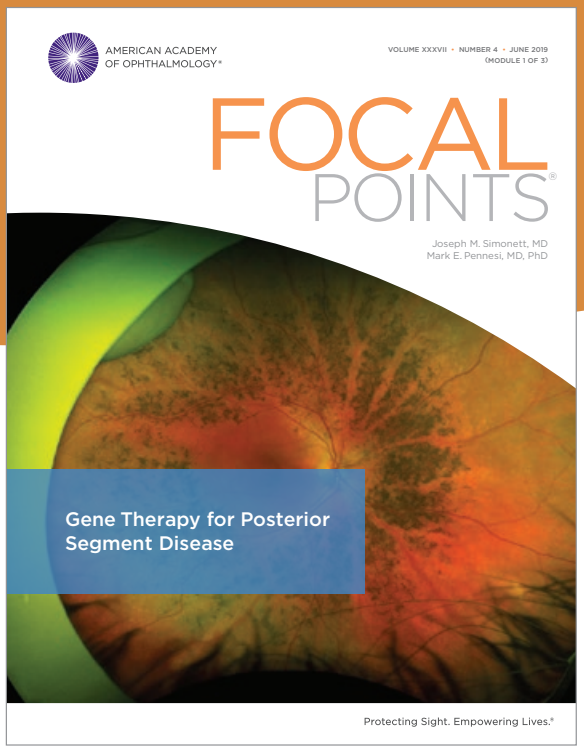

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Diabetic Retinopathy Tx: A Role for Fibrates and Statins?

Today's ophthalmologists have good treatment options for the advanced stages of diabetic retinopathy (DR)—laser, intravitreal injection, and vitrectomy—said Eugene Yu-Chuan Kang, MD, at the Chang Gung Memorial Hospital in Taiwan.

However, these treatments can be onerous, invasive, or costly. "We need something with few side effects that's inexpensive and can be given widely," noted Emily Y. Chew, MD, at the NEI.

Statins and fibrates to the rescue? Could lipid-lowering drugs such as statins and fibrates fit the bill? Certainly, they are widely available and cost-effective. "You can buy a lifetime supply of simvastatin or fenofibrate for the cost of one vial of our intravitreal injections," said Sunir J. Garg, MD, at Wills Eye Hospital in Philadelphia. They do carry a risk of side effects, however (see "Caution: Drug Side Effects").

Statins and fibrates are back in the spotlight, thanks to a recent retrospective study conducted in Taiwan by Drs. Garg and Kang and their coauthors. They investigated the association between statin therapy and the development of DR in patients with diabetes and dyslipidemia and found that statin use was associated with a decreased prevalence of diabetic retinopathy.[1]

Laying the Groundwork

Statins help lower low-density lipoprotein (LDL), a culprit in the development of atherosclerosis, and the drugs are already prescribed for many patients with diabetes, said Dr. Chew. Fenofibrate—which is sometimes prescribed to patients who can't take statins—also can lower LDL.

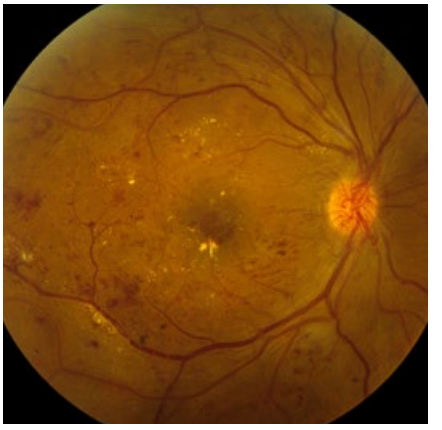
Moreover, both fibrates and statins may have multipronged effects beyond lipid control, said Dr. Kang. "These medications may also influence inflammation, angiogenesis, and cell survival."[2-4]

Interestingly, the FIELD and ACCORD-EYE studies did not confirm the effect of fenofibrate on DR to be through lipid lowering, Dr. Chew said. "We don't actually know the mechanism of action for fenofibrate in DR."

Making the case. "Years before we had statins, we saw a good correlation between lipids and eye disease in the Early Treatment Diabetic Retinopathy Study (ETDRS)," Dr. Chew said. "The higher the lipids, the higher the risk of retinopathy." With the advent of better lipid control, ophthalmologists are less likely to see eyes filled with hard exudates, she added.

The Wisconsin Epidemiology Study of Diabetic Retinopathy demonstrated that people with diabetes and visible lipid deposits in their retinas had higher serum lipid levels. It also found that increasing DR severity and hard exudates corresponded with increasing serum cholesterol, Dr. Garg said.

Other studies have indicated that lipid-lowering medicines have an effect on DR, said Dr. Garg, but it's hard to tease out the size and scope of that effect. "Does it prevent diabetic eye disease? Most of the studies right now say no," he said. "Is it useful in preventing preexisting diabetic eye disease from getting worse? Potentially."



PROGRESSION. *Neovascularization of the optic disc along with hard exudates and scattered retinal hemorrhages, seen in a patient with proliferative DR and DME. Some evidence suggests that lipid-lowering medications slow DR progression.*

Approved in Australia. Although no country has approved the use of statins for DR, said Dr. Kang, Australia approved fenofibrate for this indication in patients with type 2 diabetes in 2013, following completion of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[5] and the Action to Control Cardiovascular Risk in Diabetes-Eye (ACCORD-EYE) Study[6]—two randomized clinical trials that showed fenofibrate to be beneficial in

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **EMILY Y. CHEW, MD, SUNIR J. GARG, MD,** AND **EUGENE YU-CHUAN KANG, MD.**

Sunir J. Garg, MD

the treatment of DR. Thus far, however, no other countries have followed suit.

Three Key Studies

FIELD. This study, published in 2007, examined the effects of fenofibrate versus placebo in 9,795 patients with type 2 diabetes. The researchers found that, in addition to slowing progression of preexisting DR, 200 mg of fenofibrate per day reduced the occurrence of diabetic macular edema, Dr. Garg said.

Moreover, use of laser was reduced by nearly a third in these patients, said Dr. Chew. "In fact, all microvascular disease benefited, with a clear beneficial effect on the kidneys and a reduction in foot ulcers, for example." However, fenofibrate had no effect on cardiovascular disease outcomes.

ACCORD-EYE. This study—a substudy of the parent ACCORD study—compared the results of simvastatin plus fenofibrate to those achieved with simvastatin plus placebo. The outcomes, published in 2014, were similar to those found in FIELD, said Dr. Chew, who chaired ACCORD-EYE.

Unlike in the FIELD study, however, DR was the primary microvascular outcome in ACCORD-EYE—and the addition of fenofibrate to statin therapy demonstrated benefits for the kidneys and feet, but not for the heart, she said. The benefit of fenofibrate with regard to slowing DR progression was greatest in patients with mild retinopathy.

ACCORD-EYE "found that fenofibrate plus a statin is better than a statin alone," Dr. Kang said. Within four years, 12% of the control group progressed two or more steps on the ETDRS scale, compared with 10.6% in the statin group and 6.5% in the statin-fibrate group.[6] This translated into about a one-third reduction in the progression of diabetic retinopathy.

Taiwanese study. This population-based cohort study, published earlier this year, was conducted among 37,894 Taiwanese patients with type 2 diabetes and dyslipidemia. Of these, half had taken statins.[1]

People taking statins were less likely to have DR, said Dr. Garg. "The study also showed that statin use was associated with fewer treatments—whether laser, injections, or surgery." The researchers also found a greater association between a decrease in DR risk and the use of higher doses and longer duration of statin therapy, said Dr. Kang, which emphasizes the importance of medication adherence.

Caution: Drug Side Effects

Both fibrates and statins can cause muscle aches and liver problems, Dr. Garg noted. Other side effects linked to both drugs include headaches, abdominal pain, and nausea and vomiting. In the past, there were concerns that combining fenofibrates with statins would exacerbate muscle breakdown and fatigue, said Dr. Chew. "However, in the ACCORD-EYE Study, we found very little of that. If we saw an increase in creatinine, we adjusted the dose of the drug and the numbers went back down."

To take fenofibrate successfully, a patient needs to have regular blood work to monitor the liver and kidney, said Dr. Garg. "In cases like this, we would typically ask the cardiologist or internist to help us." The key, said Dr. Chew, is to communicate with the doctor giving the medical care. If he or she is unwilling to do the blood work, you can do it yourself.

Challenges in Moving Forward

Nuances in disease development. One challenge with these types of studies is the difficulty of detecting changes in the diabetic eye, said Dr. Garg. This was especially true before sophisticated imaging like optical coherence tomography (OCT) became available. "In addition, if a person has no diabetic eye disease at baseline and their sugar control is reasonable, their rate of developing eye disease may not be fast," he said. "In a two- to four-year period, we may not see a lot of difference in their disease."

On that note, Dr. Garg pointed out that both FIELD and ACCORD-EYE showed benefit for people who already had retinopathy, but neither showed benefit for those without retinopathy at baseline. This may have been because of the length of time needed to track the impact of treatment (as well as the time needed for retinopathy to develop), Dr. Chew said.

Need for better data. "Although some of the DR data have been compelling, they are not clean and airtight enough to really hit home with your typical ophthalmologist or retina specialist," Dr. Garg said. In addition, Drs. Garg and Kang acknowledged, their Taiwanese study is limited by its retrospective cohort design.

Need for bigger studies. What is really needed, said Dr. Garg, are larger randomized controlled trials, with sufficient power, conducted in patients with preexisting DR of various levels of severity. Ideally, too, those patients would be monitored with current imaging technologies. "But as of now, there's not a large incentive for a big pharmaceutical company to sponsor this type of trial," he said. "The drugs are inexpensive, and so no company is really pushing this."

Indeed, Dr. Chew said, what's necessary to really capture the interest and acceptance of ophthalmologists is another study conducted by ophthalmologists to test fenofibrate for this disease. A previous attempt to initiate such a trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net) fell by the wayside, she said. "We're hoping it may yet happen," she said, explaining that such a trial "would have the potential to engage 150 clinics in the network and hundreds or thousands of patients."

Current Recommendations

Given the evidence to date—and the questions that remain—should clinicians incorporate lipid-lowering drugs into their treatment plan for patients with diabetes?

Stay the course. "I would not recommend a change in practice at this time," said Dr. Garg. Controlling blood

sugar and blood pressure is what's most helpful for patients, he said. These two strategies "dwarf anything else in terms of the magnitude of importance—not just for eyeballs but for overall health."

Glucose control. Tight glucose control can reduce the risk of eye disease by as much as 70%, said Dr. Chew—and with type 2 diabetes, it can reduce its progression rate by a third.

Blood pressure control. In ACCORD-EYE, the researchers didn't find a treatment effect with blood pressure control, Dr. Chew said. However, other studies have. For example, the United Kingdom Prospective Diabetes Study (UKPDS) showed that, after nine years of follow-up, tight blood pressure control (target pressure of <150/85 mm Hg), compared with less tight control (target pressure of <180/105 mm Hg), reduced the progression of DR and reduced the risk of vision loss by 47%.[7]

Lipid control. Despite the dearth of randomized trials focusing on lipids and DR, Dr. Kang recommended that ophthalmologists emphasize lipid control in patients who have diabetes. "Ophthalmologists should encourage these patients to not only have regular eye exams but also systemic evaluations, including [analysis of] serum lipid levels."

Adherence. If medication is prescribed, it's important that the patients, family, and doctors make sure the patient takes it regularly, Dr. Kang said. "Without medical adherence, the disease can't be well controlled."

Consider fenofibrate? At this time, statins are very well accepted, said Dr. Chew, and most patients with diabetes are put on them. "The main drug in question is fenofibrate, especially since studies have not shown that it helps with cardiovascular disease," she said. "For this reason, endocrinologists and other physicians are reluctant to prescribe fenofibrate. And ophthalmologists are also reluctant to prescribe it because of the required medical monitoring."

However, in collaboration with a patient's internist, cardiologist, or other medical physician, Dr. Chew has prescribed fenofibrate for some of her patients with DR.

Diabetes statements. Although the Academy's *Preferred Practice Pattern* on DR does not contain a specific recommendation for fenofibrate,[8] the American Diabetes Association Position Statement notes that ". . . there are sufficient data to suggest developing collaboration between the ophthalmologists (eye care providers) and the medical physician to consider this treatment for people affected with diabetic retinopathy."[9]

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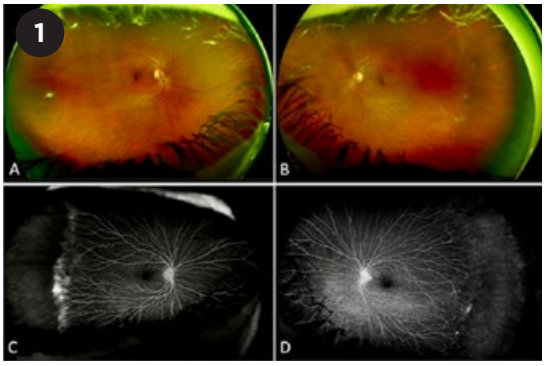
Familial Exudative Vitreoretinopathy

Familial exudative vitreoretinopathy (FEVR) is an inherited vitreoretinal disorder characterized by incomplete or anomalous vascularization of the peripheral retina. The avascular peripheral retina leads to various degrees of retinal ischemia, which can cause neovascularization, vascular dragging, radial retinal folds, retinal exudates, vitreous hemorrhages, and tractional retinal detachments (RDs). About half of FEVR cases are associated with known genetic mutations, and the etiology is unknown in the remainder.[1]

This disease entity was first described by Chriswick and Schepens in 1969, in a report of six patients from two families who had fundus findings similar to those observed in retinopathy of prematurity (ROP). In a recent multicenter investigation of 199,851 newborns who received screening ocular exams, the reported incidence of FEVR was 0.11% (219 cases).[2] The prevalence of FEVR is likely to be underestimated; vascular abnormalities in the peripheral retina may be overlooked on routine exams, and widefield fluorescein angiography (FA) is not routinely used in clinical practice.[3]

Presentation. The presentation and severity of the disease are highly variable, even among family members and sometimes between the two eyes of the same individual. Although avascular peripheral retina may be the only manifestation, some cases may advance to neovascularization, exudation, sub- or intraretinal hemorrhage, hyaloid contraction, and RD.[4] Because of the variability of expression and incomplete genetic penetrance, the disease is often misdiagnosed. It is important to distinguish FEVR from other conditions with similar findings, including Norrie disease (ND), ROP, RD, Coats disease, retrolental fibroplasia, sickle cell retinopathy, and Eales disease (see "Differential Diagnosis"). Widefield FA remains the most helpful diagnostic tool.[3]



FEVR CASE. *Fundus images of a 61-year-old woman with stage 2 FEVR. (1A, 1B) Temporal avascular retina with a vertical, white fibrovascular ridge. (1C, 1D) Fluorescein angiogram of right and left eye, respectively, showing a sharp demarcation line between vascular and avascular retina associated with vascular pruning. (See this article at aao.org/eyenet for more information about this case.)*

Pathophysiology

Incomplete vascularization of peripheral retina in FEVR is the result of developmental abnormalities.

In normal development, vasculogenesis begins when spindle-shaped mesenchymal precursor cells, migrating to the retina through the optic disc, differentiate into endothelial cells, which aggregate to form patent vessels that expand centrifugally. Next, angiogenesis occurs when sprouts of blood vessels emanate from the preexisting vascular framework, increasing the vascular density of the immature plexus and extending it peripherally. This process is mediated by vascular endothelial growth factor (VEGF) expressed by astrocytes in response to localized retinal hypoxia, which highlights the importance of VEGF in ocular vascularization.[5]

Most genes associated with FEVR affect pathways regulating the development of the secondary embryonic retinal vasculature via angiogenesis. Thus, the gene mutations in FEVR lead to incomplete or anomalous vascularization of the peripheral retina. In normal development, hyaloid vasculature forms and then regresses prior to retinal vascular development, but persistent hyaloid vasculature due to failure of regression is sometimes seen in FEVR.

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Genetics

Approximately 50% of FEVR cases have a genetic cause, and the disease can be transmitted through autosomal dominant, autosomal recessive, or X-linked patterns of inheritance. FEVR is associated with various gene mutations. Autosomal dominant FEVR, the most common inherited type, is associated with mutations in the frizzled-4 (*FZD4*), low-density lipoprotein receptor–related protein 5 (*LRP5*), tetraspanin-12 (*TSPAN12*), kinesin family member 11 (*KIF11*), and zinc finger protein 408 (*ZNF408*) genes.

X-linked FEVR and ND are associated with mutations in the *NDP* gene, which produces the norrin protein. The Wnt canonical pathway plays a central role in cell proliferation, differentiation, and migration in the body, including formation of retinal vasculature, by promoting accumulation of cytosolic b-catenin. Consequently, gene mutations that encode the Wnt receptor FZD4, coreceptor LRP5, or the ligand norrin result in retinal vascular disruption.[6]

Diagnosis

Widefield FA is the gold standard for diagnosing FEVR.[3] In pediatric patients, evaluation may require examination and imaging under anesthesia. Optical coherence tomography angiography has demonstrated parafoveal microvascular defects with vascular density correlating to vision loss in FEVR without RDs.[7]

Screening asymptomatic family members with widefield FA may aid in early detection and, if needed, treatment of FEVR to prevent progression and vision loss. It also facilitates genetic counseling for individuals of childbearing age.

Clinical features. The progression and phenotypic expression of the disease vary among individuals.[1] As previously noted, there may even be asymmetric clinical findings in the fellow eye of the same patient. Pediatric patients often have a more progressive disease course than adults, which can lead to serious, vision-threatening complications such as RD. Adults typically have a more indolent course. However, in both adults and children, progression can commence or halt at any time during the course of the disease.

Mild disease. Peripheral avascular retina can be seen vertically or in a wedge or V shape, with the apex pointing toward the macula. The peripheral avascular retina initially presents without neovascularization but can develop neovascularization or arteriovenous fistulas at the edge of the avascular zone.[4] Hyaloid remnants may be seen. Patients are usually asymptomatic at this stage and are diagnosed incidentally on fundus examination with an indirect ophthalmoscope or FA.[5]

Table 1: Staging of FEVR

Stage	Description
1	Avascular peripheral retina
2	Retinal neovascularization A. Without exudate B. With exudate
3	Extramacular retinal detachment A. Without exudate B. With exudate
4	Macula-involving retinal detachment, subtotal A. Without exudate B. With exudate
5	Total retinal detachment

SOURCE: Ranchod TM et al. *Ophthalmology*. 2011;118(10):2070-2075.

Moderate disease. Neovascularization leads to fibrous changes that can manifest as strong vitreoretinal adhesions and/or fibrovascular stalks. These fibrovascular stalks and/or vitreoretinal bands place traction on the posterior pole, pulling the macula toward the origin of the neovascularization. The traction can cause ectopic macula and may distort the optic disc, significantly affecting vision. Continued fibrovascular activity may lead to RD outside the macula, which can further drag on the posterior pole. There may be evidence of shallow intraretinal or subretinal exudation.[1]

Severe disease. Severe extraretinal neovascularization may result in subtotal macular or total rhegmatogenous and/or tractional retinal detachments. In a study of 273 eyes, 64% of FEVR patients developed RDs.[1] Some patients with severe tractional peripheral displacement of the retina develop a falciform retinal fold that originates from the optic disc and stretches across the macula. Ranchod et al.[1] reported that the majority of retinal folds were radial and were seen in every quadrant, not just temporally, as was previously believed. Radial folds are classified as dry, knifelike, and broad, and they may be associated with subretinal exudate or blood. In advanced cases, anterior segment complications including cataract, neovascular glaucoma, and band keratopathy may be present.[1,5]

Differential Diagnosis

The fundus findings in FEVR are similar to those of several other diseases. Some pointers for differentiating among them are included below.

Retinopathy of prematurity. FEVR and ROP are phenotypically similar, as patients have an area of avascular retina bilaterally and leaky peripheral retinal blood vessels. FEVR and ROP also have some genetic similarities: Four variants of three FEVR genes (*FZD4, LRP5,* and *TSPAN12*) have recently been associated with ROP.[8]

Despite similar clinical features, FEVR is classically distinguished from ROP according to whether the patient was born full term or prematurely. Further, ROP generally progresses on a predictable timeline, with retinal neovascularization occurring at approximately 37 weeks postmenstrual age followed by RD around 41 weeks. In contrast, FEVR is more unpredictable and may remain dormant throughout a patient's life or progress in childhood or adulthood.[1]

Norrie disease. ND is associated with X-linked mutations of *NDP* and presents with ocular manifestations similar to those noted in FEVR. However, ND usually has coexisting system-

ic conditions of progressive deafness and cognitive delay.

There is also a difference in the location of mutations for the norrin protein, a product of the *NDP* gene. Mutations in the cysteine residues of the norrin protein lead to ND, while mutations in the noncysteine residues lead to X-linked FEVR.

Coats disease. RDs with significant exudations in Coats disease can resemble FEVR. However, Coats is unilateral and sporadic, and it primarily affects boys, with diagnosis typically between age 8 and 16 years.

Persistent fetal vasculature (PFV). Although failure of regression of hyaloid vessels is seen in both FEVR and PFV, in the latter condition it is usually unilateral and not inherited.

Eales disease. Although they are initially asymptomatic, Eales patients typically present with periphlebitis and obliterative retinal vasculopathy affecting the peripheral retina, which can lead to neovascularization and tractional RDs.

Sickle cell retinopathy. Findings of sickle cell retinopathy include peripheral neovascular "sea-fans" and salmon patches, which can lead to tractional RDs. Systemic and laboratory workup can further differentiate this disease from FEVR.

Toxocariasis. This ocular roundworm infection forms a granuloma with a stalk that can be mistaken for a fibrovascular stalk wrapped in retinal folds found in FEVR. However, toxocariasis also has a significant component of posterior uveitis, which is absent in FEVR.

Osteoporosis pseudoglioma syndrome. This syndrome is characterized by reduced bone mineralization resulting in increased risk of bone fractures in childhood, along with an ocular FEVR-like presentation. Cognitive decline and muscle hypotonia may also be present.

Incontinentia pigmenti (IP). An X-linked ectodermal dysplasia, IP usually presents with characteristic dermatologic changes but may have retinal findings similar to FEVR. Ophthalmic manifestations are present in about one-third of cases.

Staging

Various grading systems to classify FEVR have been proposed. Initially, staging was based on clinical findings but has undergone revisions to incorporate FA characteristics and other developments.[9] Table 1 outlines a commonly used staging system.[1]

Management

Management of FEVR depends on the stage and severity of retinal findings. Stage 1 can be managed with observation for signs of neovascularization. In stages 2 to 5, the goal is to prevent the progression and sequelae of neovascularization. Laser photocoagulation and/or cryotherapy to address neovascularization are indicated in stage 2. Given that VEGF affects the Wnt/β-catenin pathway, anti-VEGF therapy may decrease hemorrhage and exudation[10]; however, this may worsen the vitreoretinal traction owing to contraction of fibrovascular tissue.

Continued fibrovascular proliferation can lead to rhegmatogenous or tractional RDs requiring surgery. Although surgical intervention is recommended for the complications of FEVR, the prognosis for improved visual acuity (VA) is guarded depending of the level of severity. In a recent study, 22 patients ages 3-6 with stage 5 FEVR underwent either lens-sparing vitrectomy, vitrectomy with lensectomy, or lensectomy alone. Final VA was tested on 17 eyes, which ranged from no light perception (NLP) to 30/200.[11] Surgical techniques include pars plana vitrectomy, scleral buckling, or a combination of both with or without lensectomy.

Because of the unpredictable disease course, risk of reactivation, and chronic nature of FEVR, lifelong monitoring with twice-yearly exams (as well as widefield FA in eyes at risk) is indicated, and treatment may be needed throughout the patient's life.

Conclusions

FEVR is a complex retinal condition that is often underrecognized and can lead to severe vision loss. Early recognition, with careful bilateral dilated exams and widefield FA, is important in making the correct diagnosis. Once there is evidence of neovascularization, laser photocoagulation treatment of the peripheral avascular retina should be initiated. Prompt treatment is aimed at preserving vision and preventing sight-threatening complications of neovascularization, including vitreous hemorrhage, RD, and neovascular glaucoma.

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EXTRA **MORE ONLINE.** See this article at aao.org/eyenet for two case studies and additional images.

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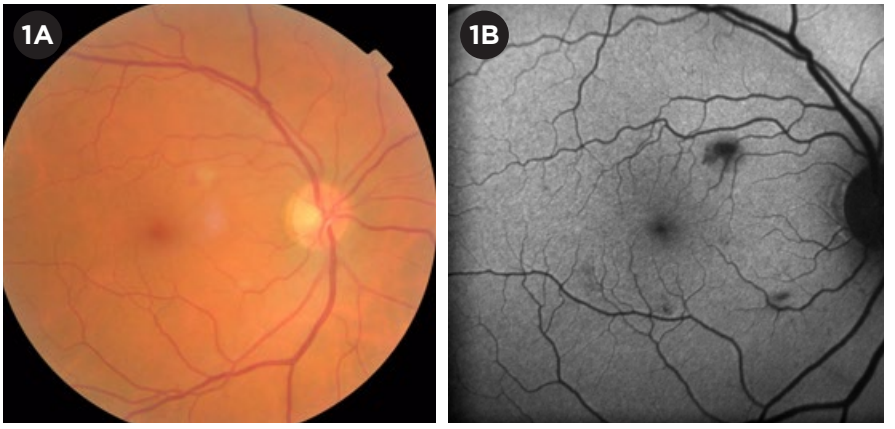
A Case of Fever and Floaters

In the middle of a hot summer in Galveston, Texas, Ellie Roberts,* a 62-year-old woman, began to develop fever, sore throat, and malaise. She presented to an urgent care physician, who presumed that she had cat-scratch disease because she was caring for several small kittens at home. However, despite six days of treatment with azithromycin, her fever still hadn't subsided, and she began to develop floaters in her left eye. She did not have headache or eye pain associated with her floaters. Mrs. Roberts became very concerned because she had read online that floaters can be a symptom of a sight-threatening retinal detachment. She urged her primary care physician to give her a referral to an eye doctor, and she subsequently presented to the department of ophthalmology at our institution.



RIGHT EYE. *(1A) Cotton-wool spot with a small hemorrhage located superonasal to the fovea and a second cotton-wool spot inferotemporal to the optic nerve. (1B) The cotton-wool spots seen in Fig. 1A caused blockage of fluorescein on angiography.*

We Get a Look

Presentation. Mrs. Roberts was visibly ill in the waiting room. By the time she came to our clinic, she had experienced fever (100-102 degrees F) and malaise for 23 days, and her floaters had been getting worse. She also reported night sweats, a 10-pound weight loss over one month, and blurry vision.

The remainder of her review of systems was unremarkable. She had no significant past medical history and no ocular history except for refractive error. She had not been taking any medications prior to her current illness.

As previously noted, Mrs. Roberts said that she loved to care for her kittens and an adult cat at home in her free time. She hadn't been able to travel lately, since she had been taking care of her ailing husband. She also mentioned that one of her neighbors had been hospitalized recently for a fever of unknown origin.

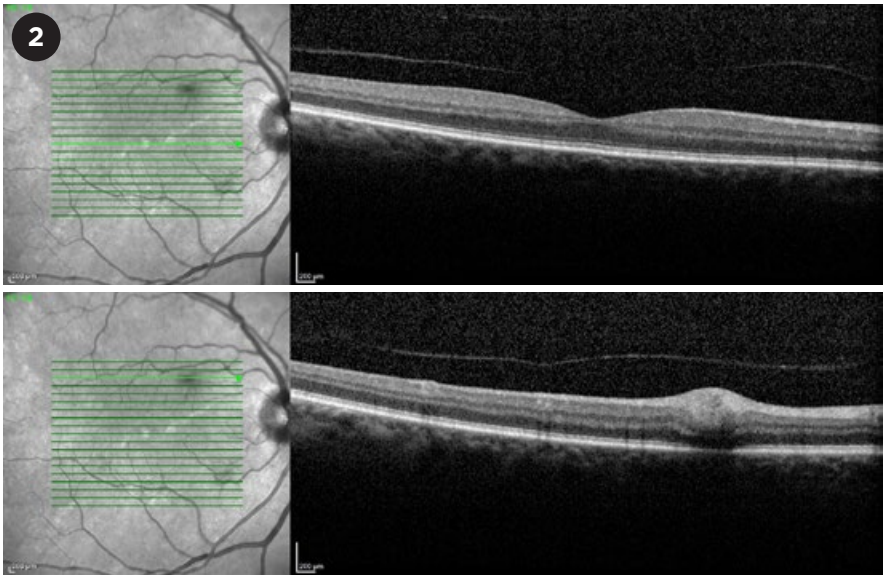
Exam findings. On examination, the patient's best-corrected visual acuity was 20/25+1 in the right eye and 20/30 in the left. Her pupils, intraocular pressures, and ocular motility were normal. She had 1+ cells in the anterior chamber and vitreous in both eyes, with vitreous debris in the left eye. Dilated fundus exam of the right eye showed two small lesions that looked like cotton-wool spots (Fig. 1A), along with a small hemorrhage. The remainder of the examination was unremarkable.

Additional observations. The two small lesions in the right eye caused blockage of fluorescein on angiography (Fig. 1B), and optical coherence tomography localized a hyperreflective lesion to the retinal nerve fiber layer (RNFL, Fig. 2). Apart from the vitreous cells and debris, posterior examination of the left eye was normal.

Differential Diagnosis

Given the presence of 1+ cells bilaterally in the anterior chamber and vitreous, we diagnosed Mrs. Roberts' ocular disease as a bilateral panuveitis. However, the more intriguing question was the underlying condition. The differential diagnosis for uveitis is long, with a wide range of etiologies, including infectious, systemic autoimmune

BY **AKSHAYA GUPTA, LANCE LYONS, MD,** AND **LARRY PUTHENPARAMBIL, MD.** EDITED BY STEVEN J. GEDDE, MD.



OCT. *Swelling of the nerve fiber layer in the right eye is seen on optical coherence tomography.*

and inflammatory, and hypersensitivity disorders. Additionally, some cases of uveitis are isolated to the eye.

Infectious etiologies. Infectious causes of uveitis include (but are not limited to) herpesvirus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), toxoplasmosis, HIV, syphilis, *Bartonella henselae,* tuberculosis, West Nile virus, and *Rickettsia* species.

Systemic autoimmune and inflammatory causes. Diseases associated with systemic inflammation can also cause uveitis. Some of the common culprits include sarcoidosis, multiple sclerosis, systemic lupus erythematosus, Vogt-Koyanagi-Harada syndrome, and Behçet syndrome.

Hypersensitivity reactions. Certain drugs and drug classes can incite uveitis, including rifabutin, cidofovir, fluoroquinolones, bisphosphonates, and BRAF inhibitors.

Disorders restricted to the eye. A number of conditions that cause uveitis have no extraocular manifestations. These include pars planitis, birdshot chorioretinopathy, and sympathetic ophthalmia.

Neoplastic. Intraocular malignancies including lymphoma/leukemia, melanoma and retinoblastoma can present with signs and symptoms resembling uveitis. These are frequently termed "masquerade syndromes."

Idiopathic. Even after extensive workup, the etiology for uveitis is never found in many instances. Up to 30% of uveitis cases do not have apparent etiology and are classified as idiopathic.

Making the Diagnosis

A careful history and review of systems can aid in narrowing the extensive differential diagnosis for panuveitis. In Mrs. Roberts' case, the absence of any significant past medical history, including autoimmune disease or prolonged medication use, pointed us away from systemic inflammatory or hypersensitivity etiologies. In addition, her concurrent systemic symptoms suggested an infectious cause, rather than a disorder restricted to the eye, so we tailored our workup toward those conditions in the differential.

Laboratory testing. Before we examined Mrs. Roberts, she was already being worked up for a fever of unknown origin and had undergone a battery of tests. These included complete blood count, metabolic panel, urinalysis, QuantiFERON-TB Gold, antinuclear antibodies, erythrocyte sedimentation rate, rheumatoid factor, lactic dehydrogenase, CMV immunoglobulin M (IgM) and polymerase chain reaction, and creatinine kinase results, all of which were normal.

After we saw her in clinic and established a diagnosis of panuveitis, we recommended additional testing based on our differential, including HIV, syphilis IgG, EBV, and *Bartonella* serology, all of which were negative. The infectious disease physician recommended a chest, abdomen, and pelvis computed tomography scan, which revealed right thoracic inlet, mediastinal, and right hilar lymphadenopathy, with the largest lymph node measuring 1.5 × 2.6 cm in the right paratracheal region and 1.3 × 2.7 cm in the right lower neck.

Uncovering the cause. The Galveston epidemiology department contacted Mrs. Roberts regarding the possibility of murine typhus because of its endemic nature in this part of the country, her exposure to cats (and therefore fleas), and her neighbor with similar symptoms. She was finally tested for *Rickettsia typhi,* for which she had positive IgG and IgM titers.

Treatment

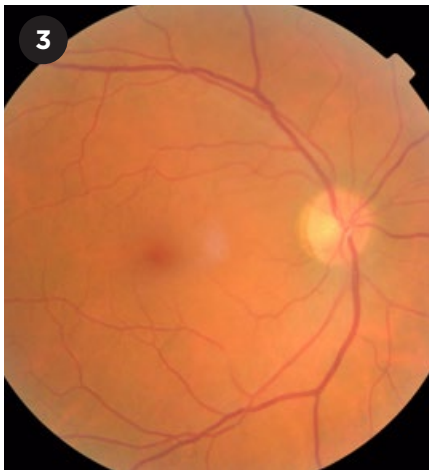
Mrs. Roberts was treated with doxycycline 100 mg every 12 hours for seven days. About two weeks after she started treatment, her symptoms resolved; she no longer had fever, malaise, or floaters, and she began to regain the weight she had lost during her illness. The cotton-wool spots and the hemorrhage had also resolved (Fig. 3).

Discussion

Rickettsia typhi is an obligate intracellular organism that causes murine typhus and is typically spread through the feces of infected fleas. Rats, opossums, and even domestic cats are reservoirs for the disease. Murine typhus is especially common in coastal and port cities. In the United States, cases of murine typhus have been reported in central and south central Texas and in Los Angeles and Orange counties in California.[1] The disease frequently occurs in epidemics; however, because the symptoms are nonspecific, it is difficult to diagnose and is substantially underreported.[2] Clinical features of the disease combined with epidemiologic data are key to making the diagnosis, which can be confirmed with serological evidence using indirect immunofluorescence assays.

Systemic involvement. Murine typhus has a six- to 14-day incubation

Amber Ovalle, COA



RESOLUTION. *(3) After treatment with doxycycline, the cotton-wool spots in the right eye resolved.*

period before the onset of symptoms, which may include high fevers, myalgias, fatigue, and a rash. The rash, if present, is typically located centrally on the trunk. Multiple organ system involvement has been documented, with abnormal lab findings for hematologic, respiratory, hepatic, and renal systems.[3]

The most common manifestations are fever (96% of patients), headache (75%), and chills (66%), with a rash occurring in slightly over half of cases. Gastrointestinal symptoms may include nausea (48% of patients), vomiting (40%), and diarrhea (21%).[2] Although the disease is typically mild, it can lead to hospitalization (10% of patients) and death (4%).[4]

Ocular findings. The *Rickettsia typhi* organism has a predilection for vascular endothelium, specifically retinal vessels, which explains its wide array of ocular manifestations.[5] Retinal findings that have been described previously include areas of retinal whitening and hemorrhages. There are no apparent choroidal findings on clinical examination, but hypofluorescent dots have been reported on fluorescein angiography and indocyanine green angiography. Optic nerve involvement has also been noted, in the form of optic disc staining, optic edema, or optic neuritis.[4] Although the previous literature has not documented changes on optical coherence tomography, this patient's imaging demonstrates that a swelling of the RNFL may be attributable to murine typhus uveitis (see Fig. 2).

Treatment. Early initiation of antibiotics is crucial and yields better outcomes for patients with severe disease. Treatment is typically initiated empirically based on clinical findings. However, signs and symptoms of the disease can be nonspecific, and results of immunologic testing may take two to three weeks to return.[6] Ocular examination can help to provide valuable information for atypical presentations of rickettsial disease while the serologies are pending.

Doxycycline is the drug of choice for rickettsial disease (100 mg twice a day for seven to 10 days). Other tetracyclines can also be effective in treating murine typhus. In children and pregnant patients, macrolides may be used in lieu of tetracyclines.[6]

*Patient name is fictitious.

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Financial disclosures: None.

Morning Rounds: 2019 in Review

Tackle this year's medical mysteries. View this article online, where you'll see links to all the case reports that *EyeNet* has published so far in 2019.

The Curious Case of Cysts and Sight. After a presumed ocular migraine, the 28-year-old's vision became hazy (January).

A Case of Pixelated Vision. The 65-year-old insisted that he had a 10%-15% reduction in vision, which he described as pixelated (February).

The Case of Red Eyes and Red Ears. The 57-year-old's eyes were red, painful, and photophobic; his ears, painful and tender (March).

A Mysterious Eyelid Mass. The 47-year-old noticed an area of fullness in her right upper eyelid. She began to feel uneasy as the mass grew and became readily visible. Then it started feeling tender to the touch (April).

The Case of the Blind Bibliophile. The 64-year-old had experienced a month of rapid decline in vision, followed by gradual deterioration. Five months later, reading was impossible (May).

The Eyelid Lump That Wouldn't Go Away. The patient was frustrated with his year-old lump that had not responded to topical antibiotics or steroids (June).

The Case of the Double-Edged Protector. The root cause of a surgical oversight (and the swiss cheese metaphor for medical mishaps) (July).

The Horticulturist With Blurry Vision. This horticulturist's case underscores the importance of a thorough history (August).

The Swollen Eyelid That Kept on Swelling. Despite use of erythromycin ointment, the young boy's eye became even more swollen and was now painful (September).

The Case of a High School Graduate With a New Blind Spot. The 18-year-old described an egg-shaped black dot just off-center in her right field of view (October).

NEXT MONTH: A Puzzling Pediatric Tumor. The eight-year-old had a painful foreign body sensation in her right eye and, for the previous few weeks, hadn't been able to see her alarm clock with her left eye. She had a history of accommodative esotropia with 20/20 vision in both eyes.

Amber Ovalle, COA

Private Equity and Ophthalmology

Explore Your Options, Beware the Hazards

From choppy regulatory waters to rapidly increasing costs, there are many reasons to ponder your economic future. Should you stay the course? Consolidate your practice with others? Or seek a deal with private equity? There is much to consider.

By Lori Baker-Schena, MBA, EdD

PROPONENTS OF PRIVATE EQUITY say that it can provide capital, economies of scale, enhanced management expertise, and extra leverage when negotiating with payers. Critics worry what its emphasis on profitability might mean for patient care as well as for physician and staff job satisfaction. And many ophthalmologists remember the physician practice management companies (PPMCs) of the 1990s, whose business model turned out poorly for investors and physicians alike (see "PPMCs in the 1990s," page 43). Will today's private equity firms prove to be more sustainable?

Private Equity Today

Why private equity is looking to make deals. "Ophthalmology is attractive to private equity: It has all aspects of care, from general to subspecialty, with an elective cash pay component," said Mark D. Abruzzo, JD, with Wade, Goldstein, Landau & Abruzzo in Berwyn, Pennsylvania. In addition, the specialty is technologically advanced and offers ambulatory surgery center opportunities.

An early participant in the current wave of acquisitions. Gary I. Markowitz, MD, founder, and now director emeritus, of the Delaware Eye Care Center in Dover, Delaware, was involved with the first wave of the most recent private equity movement. He sold his practice to EyeCare Service Partners (ESP) in 2014. "Everything was centralized to cut overhead, from billing and human resources to the optical lab, and this consolidation produced cost savings," explained Dr. Markowitz, who now represents ophthalmologists in sales to private equity firms.

Private equity's surging interest. After ESP's early success, other private equity firms came into the market. "Today, they number 30 to 35. In the meantime, the valuations increased," noted Dr. Markowitz.

This uptick in private equity interest was confirmed in a recent study. "We found that acquisitions of ophthalmology practices by private equity firms have increased dramatically over the past two years, with the majority of the activity concentrated in the eastern United States and Midwest," said Gary J. Lelli Jr., MD, at Weill Cornell Medical College in New York City. A dearth of peer-reviewed research prompted Dr. Lelli to join his colleagues in studying private equity acquisitions in ophthalmology. They presented their findings in a poster at this year's annual meeting

Pat Kinsella

of the Association of Research in Vision and Ophthalmology (ARVO).[1]

Profit is paramount. "Private equity companies are looking for return on investment, and their ultimate goal is to flip the practice within five years," said Arvind Saini, MD, MBA, with Integrity Eye, a practice in Escondido, California. "There is a ticking clock, and they have to show profitability to their institutional investors. They are not necessarily making business decisions with the same motivations as physicians." Dr. Saini has a unique perspective on the private equity trend, as he previously earned a Wharton MBA with classmates who aimed to work in private equity. He also worked with a management company that purchased and managed nonophthalmology physician practices.

EBITDA is used to determine acquisition price. Private equity determines its acquisition price for a practice based on a multiple of the practice's adjusted EBITDA, which is an acronym for earnings before interest, taxes, depreciation, and amortization (see "EBITDA Primer"). In 2014, platform practices—defined as practices with more than $2 million of adjusted EBITDA—were bought at about 6 times EBITDA, and the smaller practices—with substantially less than $2 million of adjusted EBITDA—were acquired at 2 to 4 times EBITDA, said Dr. Markowitz. Today, the large platform practices are paid multiples of the adjusted EBITDA ranging from 8 to double digits; smaller practices are paid multiples of 5 to 8. One strategy is to merge smaller practices with a bigger "platform" practice, then find a buyer who would apply the larger multiple to the pooled EBITDA of the merged practices. "It is all part of the plan to grow, repackage, and sell," said Mr. Abruzzo.

After the sale. "Ophthalmologists should prepare themselves for change once their practices are sold," said Dr. Saini. "Ultimately, meeting financial targets will be very important to a private equity company, which means that all aspects of a practice—from physician and staff salaries and benefits to capital expenditures and daily patient volume—will be scrutinized. This can have positive or negative outcomes on work culture, depending on what the practice was like prior to the sale."

Ensuring physicians keep some skin in the game. "It is very important to the private equity firms to have the doctors incentivized and pulling in the same direction," Mr. Abruzzo noted. For example, the selling owners may be required to roll back some of their sales proceeds into the entity that will now be running their practice. Nonowner associates are offered opportunities to purchase equity in these management companies as well, said Dr. Abruzzo. This will give them a share of the proceeds when private equity sells the practice. "It's all about the second sale, and they make no bones about it," he said. "The idea is to buy and then resell in five years or so at, hopefully, a higher EBITDA and higher multiple."

EBITDA Primer

Mr. Abruzzo explained that acquisition prices are based on a multiple of a practice's *adjusted* EBITDA (earnings before interest, taxes, depreciation, and amortization). For example, a smaller practice might be valued at five times its adjusted EBITDA, and a larger platform practice might be valued at up to 12 times its adjusted EBITDA.

Why adjust the EBITDA? The adjustments to the EBITDA are often referred to as "normalization adjustments." They take into account expenses and revenues that were factored into the EBITDA calculation, but they won't appear on the practice's books after the sale. Examples include one-off expenses, such as legal settlements.

Some adjustments reduce EBITDA. Suppose, for example, the practice has been getting a sweetheart deal on rent because the physician owners—via a separate legal entity—also own the building. If the rent is going to increase to market rate after the practice is sold, the buyer would want the EBITDA to be adjusted downward.

Some adjustments boost EBITDA. Typically, the selling owners' wage will be significantly lower after the sale. As this reduction in wages will increase the practice's cash flow, the EBITDA will be adjusted upward. (Most private equity companies will compensate the selling physicians at 30% of their individual collections, though collections from drugs, if applicable, and ancillary testing are excluded.)

What's in It for Ophthalmologists?

"Whether private equity is right for you depends on a variety of factors, from your age to the way you want to practice medicine," said Dr. Lelli. "Without a doubt [a sale to] private equity changes the emotional dynamics of a practice for doctors, especially if they are not majority owners."

What the research says. According to the research that Dr. Lelli and his colleagues presented at ARVO,[1] physicians are motivated to sell their practice to survive increasing local competition,

obtain access to capital and infrastructure, and counter growing administrative burdens. They also found that physicians who were able to remain majority owners, or who had a greater say in running the practice, had the more successful mergers and seemed happier. The big unknown, Dr. Lelli added, is how private equity will change the delivery of health care, "which is why research in this area is so important."

What added expertise does private equity bring to a well-run practice? "Ophthalmologists are smart. They know their markets; they know their patients; and they know what makes their practices successful," said Dr. Saini. "While private equity does bring the potential for economies of scale, as well as contracting and billing expertise, ophthalmologists are selling themselves short if they think they need private equity to run their practices in the future."

Does practice management bring more stress than satisfaction? While running one's own practice may be stressful at times, ophthalmologists realize much of their job satisfaction comes from their ability to control their work environment and create a culture of community for patients and staff members, said Dr. Saini.

A Grueling Process

The best thing you can do when considering private equity is to conduct your research and proceed with caution, Dr. Markowitz said. Here are some key stages of the private equity transaction:

- It starts with extensive internal discussions in the practice, followed by vetting and hiring of advisors.
- The physicians must then think about "marketing" their practice to potential buyers.
- Nondisclosure agreements are signed.
- The private equity firm reviews the practice's financial information to derive a value and offer a price.
- Eventually a letter of intent is signed, followed by extensive due diligence (see page 49) by both parties.
- A Quality of Earnings review takes place, as part of the above due diligence, to be sure that the financial information that the private equity firm used to calculate the adjusted EBITDA was accurate.
- Formal transaction documents are negotiated, and a formal purchase agreement is signed.
- Between signing of the purchase agreement and closing, other ancillary agreements—such as employment agreements and lease assignments—are negotiated.
- The deal is closed (ancillary agreements signed, price paid), and the transition starts.

PRIVATE EQUITY AT THE MID-YEAR FORUM (MYF). *Private equity has been a recurring topic at the Academy's MYF and was discussed at this year's forum by (top row, left to right) Dr. Wiggins, Kimberly A. Drenser, MD, PhD, and Dr. Saini, along with (bottom row) Dr. Markowitz, Dustin C. Carter, and Dr. Epley. Don't miss MYF 2020 (aao.org/myf) April 22-25, 2020, in Washington, D.C.*

Case Study: A Small Pediatric Practice

Pediatric ophthalmologist K. David Epley, MD, was not looking to be purchased by a private equity firm. Since 2008, he had been building his Kirkland, Washington, practice, Children's Eye Care, from the ground up—incorporating play areas and movie rooms to decrease the anxiety for his young patients.

Yet over the years, several different entities approached him, including private equity firms, a physician services group, and a hospital. "Ours is a small practice, with 10 employees. We were happy and everything was working smoothly," Dr. Epley recalled. "Yet we were thinking about our future, the growth of our practice, and, eventually, a retirement strategy."

In need of capital. Dr. Epley noted that his practice was "bursting at the seams" and he wanted a way to raise capital without taking out a million-dollar loan. He also did not want to be acquired by a private equity firm that would turn around and sell the practice again in five years.

Due diligence. After a yearlong due diligence process, which included intense negotiations involving salary, purchase price, and other contract details, Dr. Epley sold the practice in March 2018 to a private equity firm that was merging different specialties to help staff neonatal intensive care units. "We felt it solidified a niche, and we were its third metro area—Dallas, Las Vegas, and now Seattle—and thus we would be a part of their long-term expansion."

After the sale, a bumpy transition. As of August 2019, the practice continues to experience transition challenges. "While the sales team for the com-

David Hathcox Photography

pany was organized, the implementation team was not. Consequently, there were a lot of hiccups in the first year," Dr. Epley noted. He attributed some of the issues to the company's lack of knowledge about running ophthalmology practices, from vision plans and optical retail operations to software and electronic health records.

Biggest speedbump: new software. "The most stressful aspect of this has been transitioning from our software to the company's software so that the organization can make data decisions about how we are doing," Dr. Epley said.

Financial security. While there have been some frustrating moments, Dr. Epley noted several upsides to the arrangement, including the purchase of assets that gave the physicians money to invest in their retirement, along with stock options.

Increased support and improved benefits. "The company is big, with 35,000 employees, so it gives our staff plenty of room to grow and a path to leadership," said Dr. Epley. "We have great tech support whenever we need it and educational opportunities that we didn't have before. Our benefits package is much better than what we were providing, including an improved health care plan, 401K, and employee stock options."

Optimistic about the future. Ultimately, said Dr. Epley, the private equity acquisition has taken his practice to higher levels without personal or financial risk. "We are still in the middle of this transition and hope that it will be completed by 2020. And I see the waters calming, with a positive long-term result."

Case Study: A Large, Growing Practice

Minnesota Eye Consultants (MEC) in Bloomington—a practice with more than 350 employees, five offices, and four ambulatory surgery centers—had considered being acquired by a private equity firm for several years. Reductions in reimbursement and the increasing cost of technology had made such a deal seem increasingly appealing, said Elizabeth A. Davis, MD, who is a partner at the practice.

Due diligence. After an exhaustive 18-month due diligence process, in 2017 the partners chose the private equity firm that most closely aligned with MEC's vision and values.

After the sale, no interference in clinical care. "Two years later, we haven't experienced any direct impact on patient care, and our clinical decisions are the same. Thus far, we have not been told to change our treatment approaches, and we certainly hope that won't change going forward," said Dr. Davis. "This is why choosing the right private equity group is so important. These firms need to stay in their own lanes—otherwise they will derail their own success. And success is not only increased revenues but also having happy doctors, happy staffs, and happy patients."

LEAVING A PRIVATE EQUITY PRACTICE. *At MYF 2019, Dr. Saini urged young ophthalmologists to consider the repercussions of joining a private equity practice: If you have equity, is there a difference in your class of stock? If you leave the practice, how do you cash in on that equity? And how would the noncompete agreement impact you, given that the entity might extend across state lines?*

Fewer practice management responsibilities. The partners at the practice no longer call all the shots when financial or management decisions must be made, said Dr. Davis. "Now we still have monthly meetings of a governance committee, but the day-to-day operations are less in our hands."

More number crunching. The private equity firm provides daily reports on every single aspect of the practice, including the number of patients seen, number of surgeries, and how these data compare to the budget and year-over-years. "It is a financial analysis to a level that we never came close to doing, helping us to increase productivity and reduce overhead," Dr. Davis said.

The changes have involved pros and cons. On the one hand, it has been a huge adjustment to transition from controlling every management decision of the practice to not being involved in the daily operations, said Dr. Davis. On the other hand, the private equity firm has "removed the headache—and risk—involved with practice management," allowing the physicians to focus on patient care. The equity firm also gives MEC an edge when negotiating with insurance companies and provides more capital for growth.

Case Study: Give Private Equity a Second Chance?

Despite Dr. Wiggins' ill-fated experience 20+ years ago (see "PPMCs in the 1990s," next page), he and his partners recently took a year to explore private equity opportunities. "We found that these companies seem to be better capitalized now, offering much more cash in these deals, whereas the 1990s deals were stock heavy," he said.

Private equity's allure. "They were also making

David Hathcox Photography

the same arguments—increasing efficiency and bringing down costs through economies of scale," said Dr. Wiggins. "And that is the appeal because of current reimbursement pressures and increasing regulations as our costs continue to increase."

Considering the cons. Dr. Wiggins and his partners were concerned about the downsides to private equity arrangements. Of these, the biggest would be the loss of autonomy. Another would be decreased influence on the culture of the practice. In addition, because of the broad range of physician ages in the practice, it was clear that the senior partners would come out better financially while assuming less risk. This is because their time horizon was shorter than that of their younger colleagues.

"We were also concerned about the uncertainty when the practice is sold again by the private equity firm," Dr. Wiggins explained. "Ultimately, we felt that we are a successful practice, really didn't need new capital, and wanted to remain independent, and we decided against it."

The Generational Divide

A private equity acquisition affects older and younger ophthalmologists differently, said Dr. Davis. While those close to retirement are generally pleased with the arrangement, there is concern among the youngest partners about impact on future income. "Since you own less of the practice, going forward your income is reduced," he said.

Dr. Saini pointed out that while private equity may work out for some, "there are younger ophthalmologists who may find themselves working for practices that are less interested in long-term strategic decisions and instead are more focused on the short-term sale of the practice." Dr. Saini serves on the Academy's Young Ophthalmologist (YO) Committee, where he has spoken to many YOs about their experience working for private equity–purchased practices. "Without motivated younger associates," said Dr. Saini, "many practices will struggle. Senior ophthalmologists whose practices have been acquired by a private equity firm must figure out how to engage their younger

PPMCs in the 1990s

To many ophthalmologists, the current private equity activity in ophthalmology feels like déjà vu. In the mid-1990s, physician practice management companies (PPMCs) raised billions of dollars to invest in physician practices. However, the bubble burst within a few years, and the model collapsed due to a dwindling secondary market for the purchased practices and poor investment returns to equity shareholders and physicians. By 2002, eight of the 10 largest publicly traded PPMCs had declared bankruptcy.

Dr. Wiggins lived through the era.

"At the time, people were turning to PPMCs for different reasons," he recalled. "My partners and I were young and weren't looking to get a payout and retire. Instead, we sought out PPMCs to keep our practice strong for our entire careers. Managed care was growing, and there was a concern we wouldn't have access to contracts if we continued as a single practice."

Dr. Wiggins' practice was bought by a PPMC and received a substantial component of the purchase as stock in the new company, as well as cash and debt. The PPMC's ultimate goal was to grow the company as big as possible, take the company public, and then make money in the stock sale.

But within a few years, the physician owners realized they were not receiving the value they expected either in terms of management expertise or additional contracts.

"Eventually, we purchased back our practice, which cost us money," Dr. Wiggins said. "We got to keep the stock we had in the company, but by the time we sold, the price of the stock had decreased tremendously. I eventually ended up with a worthless stock certificate. This experience for me was a motivation to go back to school and enroll in an MHA program."

LESSONS LEARNED FROM THE 1990S. *Speaking at MYF 2019, Dr. Wiggins said that for private equity's current business model to be successful, firms must: 1) provide value to physicians in terms of income prospects and reduced administrative burden; 2) develop a model with effective governance that aligns incentives and engages physicians; and 3) ensure that the new entity thrives in the local market.*

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physicians to go the extra mile—even though they are an employee versus building their own practice with sweat equity."

What's Down the Line?

Narrowing margins. When we look at sustainability, it is important to note the high prices that private equity is paying for practices, said Dr. Markowitz. "So when they do sell them, their profit margins will be smaller. Also, the larger number of acquiring firms means more competition."

Much uncertainty. The private equity trend is so new—and the health care marketplace is so uncertain—that there is no way to make concrete predictions on results or ramifications five or 10 years down the road, said Mr. Abruzzo. "I wish I had a crystal ball," he said. "Who will be the purchasers this second time around? I question whether there will be a market then—or, at least, a sufficient market. And if there isn't, will these private equity firms have the stomach to hold on to these [practices]? Probably not. And if not, where do things go from there?"

Practice consolidation. "One trend is certain," Mr. Abruzzo said. "Consolidation of ophthalmology practices is here to stay. It really was starting to happen anyway, but this wave of private equity acquisitions has accelerated consolidation 10-fold.

THE GENERATIONAL DIVIDE. *Senior physicians near retirement may be keener than their younger colleagues on a private equity deal.*

And interestingly, when practices merge, they become bigger targets for private equity acquisitions."

1 O'Donnell EM et al. Private equity acquisitions in ophthalmology in the United States. Poster presented at: ARVO Annual Meeting; May 1, 2019; Vancouver, British Columbia, Canada.

Further reading. Want to grow your practice without private equity? For a brief overview of your options, see this article at aao.org/eyenet. For a more detailed look, see the December *EyeNet*.

Meet the Experts

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Elizabeth A. Davis, MD, is a cornea, cataract, and refractive surgeon and partner of Minnesota Eye Consultants in Bloomington, Minn. *Relevant financial disclosures: None.*

K. David Epley, MD, is a pediatric ophthalmologist with Children's Eye Care in Kirkland, Wash. *Relevant financial disclosures: None.*

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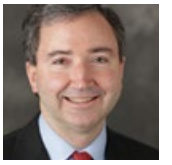
Gary Markowitz, MD, is director emeritus at Delaware Eye Center and Blue Hen Ambulatory Surgical Center in Dover, Del. He currently consults with and represents ophthalmology practices in their sales to private equity and is president and CEO of SuperVision Advisors. *Relevant financial disclosures: SuperVision Advisors: C,O.*

Arvind Saini, MD, MBA, an owner of Integrity Eye (formerly Hidden Valley Eye Associates) in Escondido, Calif. *Relevant financial disclosures: None.*



Robert E. Wiggins, MD, MHA, 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.*

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

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** Market Scope's 2018 Global Ophthalmic Laser Market Report

Take the Chart Coding Challenge: E&M or Eye Visit Code? What Level?

It is the challenge that ophthalmologists and their staff face each day: Should the exam be submitted using an Evaluation and Management (E&M) code or an Eye visit code? And what level of exam does the documentation support? Test your knowledge with two scenarios.

Exam 1: Commercial Payer With a Vision Plan

A new patient presented with complaints of blurry vision in both eyes. The 43-year-old man said that this came on gradually over the previous three days, and it was affecting both distance and near vision.

Review of systems. Ten body systems reviewed. All normal.

Past history. Not taking any medications. Has worn glasses since he was 7 years old. No family history issues. Drinks socially.

Vision exam. A refraction showed that there was a small change from the prescription of the glasses that he was wearing. All 12 elements of the exam were performed through dilated pupils. IOP was 35 mm Hg in both eyes. Gonioscopy revealed that his angles were open. Cup-to-disc ratio was 0.7 in both eyes. An order was placed for visual field 30-2 plus optic nerve photos in both eyes within the week.

Diagnosis. Primary open-angle glaucoma in both eyes, indeterminate stage.

Dissecting Exam 1

Breaking the exam down as shown below can help you to determine which code you should submit.

- Commercial insurance
- New patient exam
- Chief complaint: Blurry vision
- History of present illness (HPI) elements:
  - Timing—gradual
  - Location—both eyes
  - Duration—past three days
  - Context—distance and near
- Review of systems (ROS)—10 systems
- Past, family, and social history (PFSH):
  - Past history—no medications
  - Family history—none
  - Social history—drinks socially
- Examination:
  - Refraction performed
  - All 12 elements of the exam are performed through dilated pupils
  - Gonioscopy performed
  - Documented order for VF 30-2 and optic nerve photos
- Treatment plan initiated

Type of history. The HPI, ROS, and PFSH would support a history component that is considered comprehensive.

Type of exam. If you submit an Eye visit code, it would be considered a comprehensive exam. If you submit an E&M code, you would only be able to report a detailed exam because you didn't document an assessment of mental status (orientation to time, place, and person, and/or the patient's mood and affect).

Medical decision-making. The medical decision-making had a moderate level of complexity.

Claim submission. The level of exam that you can report will depend on the types of history, exam, and medical decision-making that your documentation supports. In this case, you can submit CPT code 99203 for a level 3 exam of a new patient, plus CPT codes 92015 and 92020 for the refraction and gonioscopy, respectively.

Discussion. Why report the E&M code for a detailed exam (99203) rather than the Eye visit code for a comprehensive exam (92004)? As with many commercial plans, this patient's vision benefits reserve the Eye visit codes for routine exams and the E&M codes for medical exams. Note: If you are audited on the subsequent exam, be sure to include the physician order for the delegated testing services from this exam documentation when responding to the auditor.

EXTRA **MORE ONLINE.** See this article at aao.org/eyenet and tackle the chart for Exam 2: An established patient complained of morning crusting on her eyelids and a burning sensation.

FURTHER READING. Visit aao.org/eyenet/archive and read "E&M Codes Versus Eye Visit Codes: Here's What's New for 2019" (April, Savvy Coder) and "Nine Scenarios When You Should Not Use an Eye Visit Code" (September, Savvy Coder).

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

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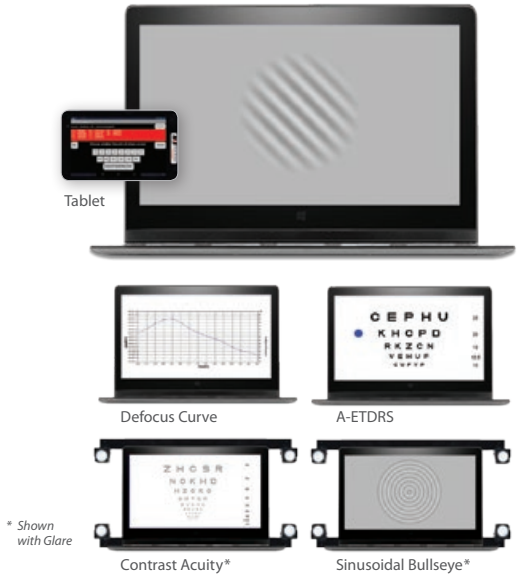

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Considering a Private Equity Deal? Due Diligence Is Crucial

For an ophthalmology practice, the importance of due diligence when considering a private equity acquisition cannot be overstated. "I've spoken to a lot of upset people, who were looking to grow, thought they found a good business model with a lot of capital, but eventually had a bad experience, some of which can be attributed to not doing their due diligence on the front end," said Dustin C. Carter, at M&M Eye Institutes in Prescott, Arizona.

Be on your guard. "A lot of physicians believe they are business-savvy people," noted Kimberly A. Drenser, MD, PhD, a retina specialist in Royal Oak, Michigan. "Yet when dealing with a private equity sale, it becomes very apparent that even the most business-savvy physician pales in comparison to the expertise and background of the different financial entities involved in the process. That puts doctors at risk, which is why due diligence is vital," said Dr. Drenser, who, as *EyeNet* goes to press, is deep in that process with multiple private equity firms.

Know what you want. A great deal of self-reflection is also necessary to determine why the practice wants to sell, what monetary compensation it expects, and what the culture will look like after the sale. The answers to these questions will help the practice find a firm with values that align with its own.

Be Ready for a Marathon

Dr. Drenser warns ophthalmologists to be emotionally and mentally prepared for a marathon. "It's like having a second full-time job, and it is a lot of work just to get to the point of deciding whether you want to go forward with a deal . . . and with whom," she said. "You are giving up a good 18 months of your life and a lot of time and money."

Mr. Carter agreed that it is an exhausting process. He was tasked with researching whether the practice should sell to a private equity entity or maintain the status quo. After many months of speaking to multiple groups and participating in the due diligence process with experts in the field, the practice narrowed down the finalists from seven to three. After selecting one of those three, coming to an agreement with it took yet another year.

Shop Around

"One of the biggest mistakes a practice can make is dealing directly with only one private equity firm. While this is an appealing approach because of its simplicity, it is potentially dangerous because you are only seeing one deal—and receiving all your financial advice from the very buyer who gains the most," Dr. Drenser said.

Instead shop around for the ideal partner. "You want to check out all 30 or 35 firms out there, and you basically want to create a bidding war," said Gary I. Markowitz, MD, a medical practice private equity consultant in Dover, Delaware. "Ultimately, three, four, or five firms will have an interest in your practice."

Three Tips

Based on his experience, Mr. Carter suggests that you do the following:

Know your value. It is vital to understand your EBITDA (see page 40), and this can be done by partnering with investment bankers or, if you are a smaller practice, your accountant and lawyer.

Get all prospective purchasers on the same schedule. Try to get all the private equity companies to reach deadlines in unison. For example, they should provide letters of intent as close in time as possible. This ensures good faith practices in the negotiating stage

Watch your money! Mr. Carter has heard horror stories of physicians who received payouts from private equity groups in the form of stock. "However, they were not aware that there can be different classes of stock—so when the time came to cash out the stocks, they did not get what was expected. In some cases, they got far less than other stockholders," he said. "So be sure to research every single detail of the deal."

BY LORI BAKER-SCHENA, MBA, EDD, INTERVIEWING **MARK D. ABRUZZO, JD, DUSTIN C. CARTER, KIMBERLY A. DRENSER, MD, PHD,** AND **GARY I. MARKOWITZ, MD.**

Get Experts on Your Side

Dr. Drenser recommended hiring experts to help you navigate a rigorous due diligence process right from the beginning. "While it may be more expensive on the front end," these experts "can save you from making poor decisions while helping you get the best deal," she said.

These experts include the following:

Third-party brokers. Much like real estate agents, these brokers earn their money on the back end of a deal. They do the background search on the private equity companies. Once the practice value is determined and the full package is created, they will shop your practice around to those firms.

Investment bankers. They serve as financial advisors and can help practices explore pretransaction, process, and operational and transitional issues. They help the physician owners maximize the value of the transaction.

Attorneys. Legal advisors protect the interests of the selling physician. Dr. Drenser suggested looking for attorneys who specialize in health care mergers and acquisitions.

Accountants and tax professionals. They focus on helping practices with asset protection and tax structuring. Because purchase prices are generally based on a practice's EBITDA (earnings before interest, taxes, depreciation, and amortization; see page 40), accountants play an important role in determining whether the purchase price was calculated accurately and whether any extraordinary expenses should be adjusted out of the calculation (generally, one-time expenses that would not ordinarily be incurred by the practice).

Do Your Homework

Mark D. Abruzzo, JD, an attorney in Berwyn, Pennsylvania, said one of the most common mistakes practices make is not doing their homework from the very beginning. You can start by asking the following questions.

Does the firm understand how to run an ophthalmology practice? Find out what sort of experience the CEO and other key executives have, said Mr. Abruzzo. "Many of these executives have experience in health care, but many folks in health care don't understand the private practice industry and the breadth of health care regulation on a state and federal level."

Mr. Carter also urges practices to look for firms that have a track record with ophthalmology. "Risk management, regulatory requirements, contract negotiations, insurance, technology, the specific personnel—so many aspects of the business of ophthalmology are unique," he said.

What's the firm's "personality"? "Through research, you want to evaluate each firm, obtain an explanation of their process from the principals, and learn the dynamics and how the firm is run," said Dr. Markowitz. Is the firm so focused on volume, numbers, and spreadsheets that patient care may suffer indirectly? It can be disconcerting to be dealing with an entity whose primary goal is making money, when the physician owners are focused on delivering excellent patient care. "Every firm is different," Dr. Markowitz said. "While one firm might be controlling, ultimately changing the culture of your practice and causing employee termination, another entity may continue to run your practice much as you did—as it helps the practice grow."

What are the private equity company's plans for your practice? Practices need to obtain an understanding of the company's motives and its approach. "You can and should determine how their current acquisitions are doing," said Mr. Carter. "Do they have a road map outlined? Do they have the management structure in place to support growth? Is the private equity firm investing in the practice, or simply purchasing and holding until they can resell? We are seeing diversity in the long-term plans of private equity groups."

How has the firm treated your peers? "At a minimum, practices should be speaking with other physicians who have sold their practices to the private equity firm" and get their honest feedback on what it is like to work with the firm, said Mr. Abruzzo. How does the firm treat physicians and staff members, from the top to the bottom, from the providers to the line staff? "Discussion of sale terms will be off limits because formal purchase agreements generally contain confidentiality clauses. But selling physicians should be able to discuss their postsale experiences with the firm."

Mr. Abruzzo warned that this strategy, while important, can be difficult to accomplish. Private equity is keen to make sure physicians' interests are aligned with its own; consequently, your peers may be incentivized to only say good things about their experience.

Will the firm provide leadership? "The private equity firm must be able not only to manage but also to provide positive leadership to practices, especially through the changes that will occur during the merger phase after acquisition," said Mr. Carter. Has the firm exhibited such leadership with its past acquisitions?

What Next?

If you make a deal with a private equity firm, expect change. There will be changes, challenges, and difficulties during the transition, said Mr. Carter. But "be assured that with the right leadership at the helm and a cooperative spirit, you can have a successful and rewarding experience."

What if you don't pursue a deal? "Even if your deal doesn't go anywhere, you can feel good knowing that you made the best decision because you did rigorous due diligence," said Dr. Drenser.

Mr. Abruzzo is an attorney with Wade, Goldstein, Landau & Abruzzo in Berwyn, Penn. *Relevant financial disclosures: Wade, Goldstein, Landau & Abruzzo: E.*

Mr. Carter is the director of clinics at M&M Eye Institute in Prescott, Ariz. *Relevant financial disclosures: Consent Solutions: E.*

Dr. Drenser is a retina specialist with Associated Retinal Consultants in Royal Oak, Mich., and director of the Pediatric Retinal Disease Molecular Genetics Laboratory on the Royal Oak campus. *Relevant financial disclosures: None.*

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

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

Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

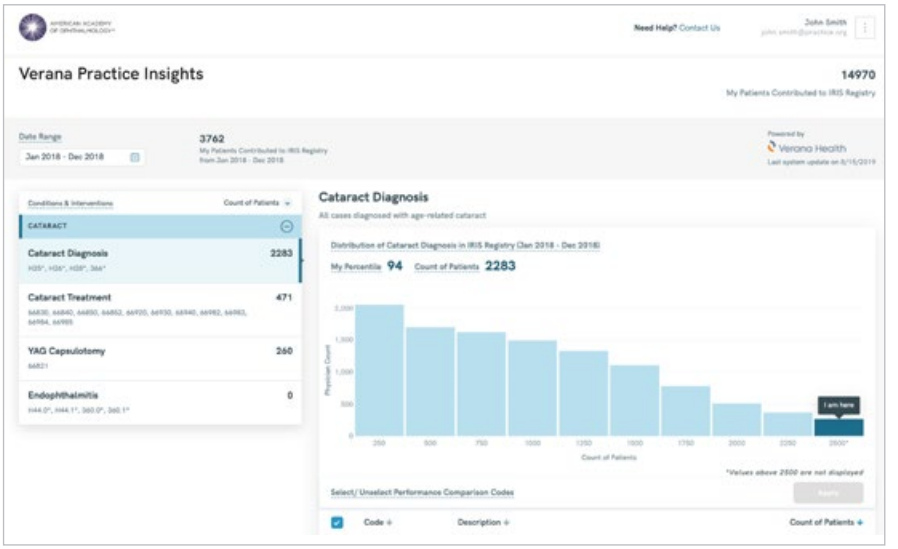
New Clinical Dashboard for IRIS Registry Users

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 dashboard feature that became available to IRIS Registry users last month. In its initial iteration, the dashboard, 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. The dashboard 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 subspecialty areas will be developed next.



NEW DASHBOARD. *The Verana Practice Insights tool allows cataract surgeons to benchmark their outcomes against those of their peers.*

Who is eligible. This free, early version of Practice Insights is available to U.S.-based Academy members who participate in the IRIS Registry via an integrated electronic health record (EHR) system.

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

Verana Health is the for-profit company to which the Academy has licensed IRIS Registry data analysis and curation. Verana makes the data analytic tools and platforms that it develops available at no charge to Academy members. For more about the relationship between the Academy and Verana Health, read the November 2018 Current Perspective column from David W. Parke II, MD, titled "All About Trust." It's at aao.org/eyenet/article/all-about-trust.

Indiana Ophthalmologists Screen Veterans

During the 2019 American Legion National Convention in Indianapolis, held Aug. 23-29, the Academy partnered with the Indiana Academy of Ophthalmology (IAO) to offer screenings and education about eye care to veterans. Seven Indiana ophthalmologists, including IAO President **Yara Catoira-Boyle, MD,** volunteered along with 12 residents and medical students from the Indiana School of Medicine to screen more than 100 veterans and their family members. **Chi Wah Rudy Yung, MD,** at Indiana University in Indianapolis, led the effort to get the residents and medical students involved in the volunteer effort.

Among their findings were cases of glaucoma suspect and suspected ischemic optic neuropathy, dry age-related macular degeneration, papilledema, and pseudotumor cerebri. In addition, volunteers identified one participant who may have had a recent stroke. Dr. Catoira-Boyle said, "This was a great opportunity for the IAO to give back to veterans and their families who have sacrificed so much for us. It was a meaningful experience for all involved."

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Next year, the Academy will continue this public service tradition and reach out to the Kentucky Academy of Eye Physicians and Surgeons to solicit volunteers for the American Legion's convention in Louisville.

Council Members Bring Cybersecurity to Forefront

Two Academy councilors teamed up to bring important cybersecurity information to Academy members in an August webinar.

The backstory. **Renee C. Bovelle, MD,** and **Lee A. Snyder, MD,** share an interest in cybersecurity, and they are both Academy councilors representing the Maryland Society of Eye Physicians and Surgeons (MSEPS). In April, they submitted a two-part Council Advisory Recommendation encouraging the Academy to 1) provide education to ophthalmologists about how to protect their most valuable electronic assets, such as patient health care data, from ransomware and 2) help spread understanding of why health care is a target. The Council approved sending this CAR to the Academy Board of Trustees, and a webinar was developed to address both recommendations.

The webinar. On Aug. 15, Drs. Bovelle and Snyder presented an Academy-sponsored webinar, titled Protecting Patients, Practice, and Profits to an audience of approximately 50 members. Dr. Bovelle, who received a master's degree in Cybersecurity Strategy and Information Management from George Washington University in 2019, said, "There has been a proliferation of cyberattacks affecting ophthalmologists. Unfortunately, we have not been adequately trained to deal with the overwhelming repercussions. Awareness of ransomware cyberattacks and understanding our responsibilities is the first step. Lee and I hope that the CME webinar will aid in empowering ophthalmologists to mitigate these threats."

The webinar was very well received, with many attendees responding to the evaluation thanking Drs. Boyelle and Lee for their effort to share the valuable information with fellow physicians. One attendee went so far as to say the

CYBERSECURITY. *Dr. Bovelle (left) and Dr. Snyder drafted the CAR that led to an August webinar on the importance of cybersecurity in ophthalmology offices.*

webinar should be mandatory for all physicians. The webinar recording is available at aao.org/annual-meeting-video/protect-patients-practice-profits-from-ransomware.

About the Council and CARs. The Academy Council is the policy advisory body to the Academy Board of Trustees. It consists of 103 ophthalmologists representing 52 state and regional societies and 30 subspecialty and specialized interest societies. A CAR is a Council Advisory Recommendation. Councilors use CARs to bring issues to the attention of the rest of the Council and, ultimately, to the Academy Board.

Learn more at aao.org/council.

TAKE NOTICE

Interested in an Externship?

Are you interested in an externship opportunity with a leading refractive, cataract, cornea, or lens-based surgeon? The International Society of Refractive Surgery (ISRS) is now offering its members a chance to bolster their clinical knowledge in imaging technology, diagnostic devices, and various surgical platforms by learning alongside colleagues through the ISRS Externship Program.

These training opportunities are offered by leading ISRS members in Africa, Asia, Europe, Latin America, and the Middle East, and they last between two weeks and three months. Stipends are available to help cover expenses such as airfare, transportation, lodging, and meals.

"The ISRS externship program granted me the opportunity to work alongside and learn from one of the world's best refractive surgeons. It also allowed me to form new friendships and future research collaborations," said ISRS member Yishay Weill, MD, a fellow at the Shaare-Zedek Medical Center, Jerusalem, Israel.

Learn more and apply by Dec. 1 for the fall program. Applications for spring start soon. Visit isrs.org/externships.

Remember the Foundation on Giving Tuesday

After your holiday shopping on Black Friday and Cyber Monday, kick off your year-end charitable donations on Giving Tuesday, Dec. 3. Entering its seventh year, this global day of philanthropy encourages donating to initiatives that are important to you. This year, consider supporting Academy programs such as the Ophthalmic News and Education (ONE) Network, EyeCare America, global outreach, and the Truhlsen-Marmor Museum of the Eye through a donation to the Foundation. Your tax-deductible gift can be made in honor or memory of someone special.

To donate, visit aao.org/foundation/giving-options.

ON LOCATION. *Dr. Weill (left) with Damien Gatinel, MD, (far right) and colleagues during his ISRS externship at the Laser Vision Institute-Rothschild Foundation Paris.*

Seeking Outstanding Ophthalmologists

Would you like to nominate a colleague for next year's Outstanding Humanitarian Service Award? The Academy must receive your nomination by March 13, 2020.

This award recognizes Academy fellows and members for outstanding contributions to humanitarian efforts, such as participation in charitable activities, care for the indigent, and community service. It acknowledges those who have performed above and beyond the normal duties of an ophthalmologist.

To obtain a nomination form, contact Member Services by phone, 866-561-8558 (toll-free) or 415-561-8581; by fax, 415-561-8575; or by e-mail, member_services@aao.org. You can also complete a nomination form at aao.org/about/awards/humanitarian.

Submit Your Research to *Ophthalmology Glaucoma*

The Academy and the American Glaucoma Society have collaborated in launching *Ophthalmology Glaucoma* to expand publishing opportunities for this booming subspecialty. Submit your research today!

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

D.C. REPORT

Academy Presses Medicare Carriers to Increase Avastin Reimbursement

WPS Health Solutions, a Medicare carrier, said it will increase its reimbursement for Avastin to $90 for participating providers, effective for claims submitted on or after June 11, 2019.

Success. The Academy urged WPS and others to increase Avastin payments to help mitigate rising costs. For the past six months, Avastin has been subject to supply shortfalls and price increases due to new federal requirements necessitating production changes to the syringes used to administer the drug.

WPS' decision follows an announcement by Noridian, which increased its pricing determination for Avastin in August in response to the Academy and the California Academy of Eye Physicians and Surgeons' data and extensive lobbying.

Repackaging Avastin with the newer Norm-Ject syringe requires more Avastin to be utilized, in contrast to the insulin syringes that outsourcing facilities had been using. This change decreases the total number of syringes that can be prepared from a single vial of Avastin. Outsourcing facilities cite this change as a key reason for the increased price of repackaged Avastin.

WPS also removed its e-news article that indicated invoices must be submitted for Avastin payments. This is significant, as a WPS plan to require Avastin invoices represented a major potential burden.

Resource from the Academy. The Academy continues to update its comprehensive resource on persisting nationwide Avastin shortages, along with information on pricing and availability. This is your one-stop shop for understanding what's changed about this important treatment.

Visit aao.org/advocacy/avastin-shortage.

FOR THE RECORD

The 2018-2019 Annual Report Is Now Available

Read the 2018-2019 Foundation annual report, *A Better Tomorrow,* to learn about the impact that member support has on the success of Academy programs. Learn about the Truhlsen-Marmor Museum of the Eye campaign, a groundbreaking donation for pediatric research through the IRIS Registry, stories of restored vision thanks to EyeCare America, and more.

Access the report at aao.org/foundation/2019-annual-report/overview-2019.

Participate in the Academy Election

The election for open positions on the Board of Trustees and voting on the proposed amendments to the Code of Ethics began on Oct. 14 and closes on Nov. 12 at noon EST. Election materials were sent to all voting Academy fellows and members. Results of the elections will be posted on the Academy's website at aao.org/about/governance/elections by Nov. 15, 2019.

ACADEMY RESOURCES

Attend Codequest 2020

Join the most knowledgeable coding experts in ophthalmology for a half-day of professional instruction in your state. Sessions will map out the latest coding updates and steer you through the complex maze of payers' rules, arriving at successful solutions for appropriately maximizing your reimbursements.

Find locations and more information at aao.org/codequest.

MEETING MATTERS

AAO 2020 in Las Vegas

AAO 2020 will take place Nov. 14-17, preceded by Subspecialty Day, Nov. 13-14, at The Sands Expo/Venetian in Las Vegas. Be part of the world's largest and most comprehensive ophthalmic meeting, offering hundreds of courses and sessions on topics ranging from cataract complications to artificial intelligence in ophthalmology.

For more information, visit aao.org/2020.

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.

To submit, visit aao.org/presentercentral.

Claim CME for AAO 2019

AAO 2019 and Subspecialty Day registrants whose attendance was verified onsite in San Francisco received an email with a link and instructions for claiming Continuing Medical Education (CME) credits online. Starting Thursday, Nov. 14, attendees can claim credits (if they did not already do so at the meeting) and obtain transcripts that include AAO 2019/Subspecialty Day credits at aao.org/cme-central. The Academy transcript will not list individual course attendance, only overall credits claimed.

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.

To learn more, visit aao.org/ondemand.

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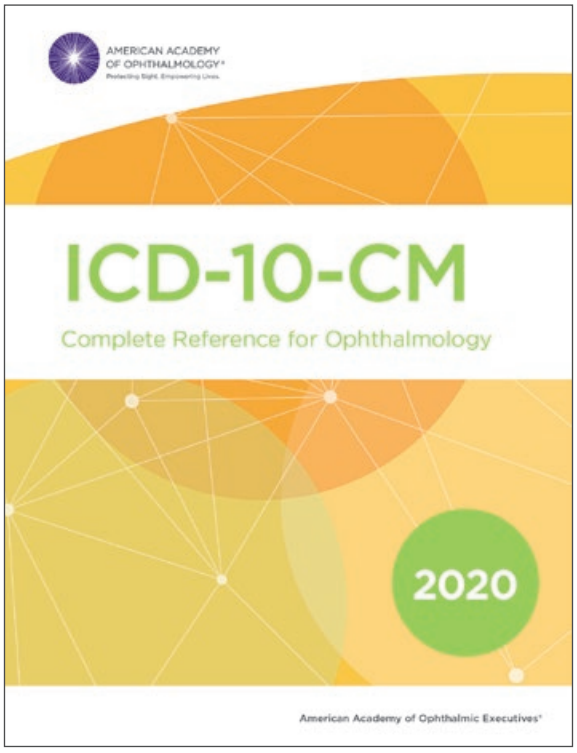

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OPHTHALMOLOGIST: GLAUCOMA SPECIALIST
UHN-Toronto Western Hospital
Kensington Eye Institute
Department of Ophthalmology & Vision Sciences
University of Toronto

The Department of Ophthalmology and Vision Sciences at the University of Toronto is inviting applications for the position of glaucoma specialist at the UHN-Toronto Western Hospital and the Kensington Eye Institute. The appointment is a full time faculty position. The effective date of this appointment is July 1, 2020.

The successful candidate will provide glaucoma subspecialty care and emergency coverage at UHN-Toronto Western Hospital and Kensington Eye Institute. The candidate will be required to participate in the teaching of medical students, residents and glaucoma fellows and will add to the body of knowledge through original research including clinical trials.

The successful candidate should possess research skills as evidenced by advanced training or a publication history. The candidate must be eligible for an academic appointment at the University of Toronto and be eligible for certification with the Royal College of Physicians and Surgeons of Canada and licensure with the College of Physicians and Surgeons of Ontario. This position is fully resourced with operating room time, clinic space, minor surgical room time and diagnostics.

Interested candidates should submit a letter of application, a curriculum vitae, and the names and contact information of three referees no later than December 15, 2019 to **sherif.el.defrawy@utoronto.ca**

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MYSTERY IMAGE

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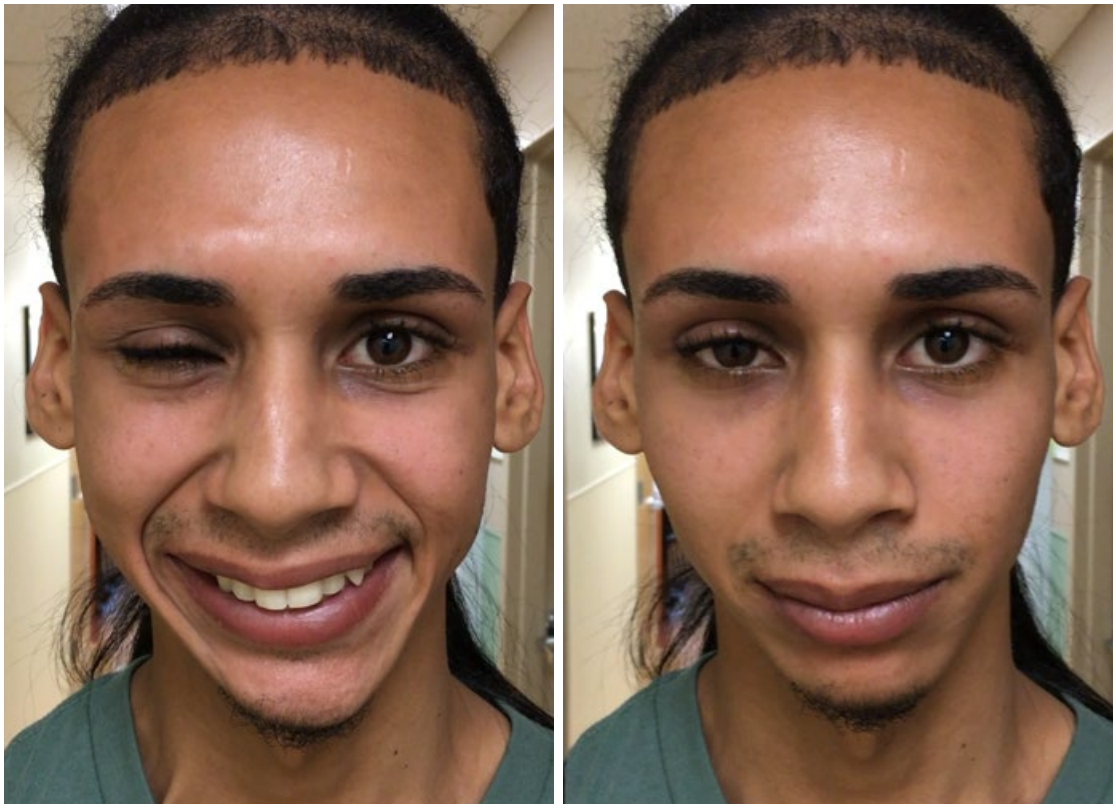


Sumana S. Kommana, MD

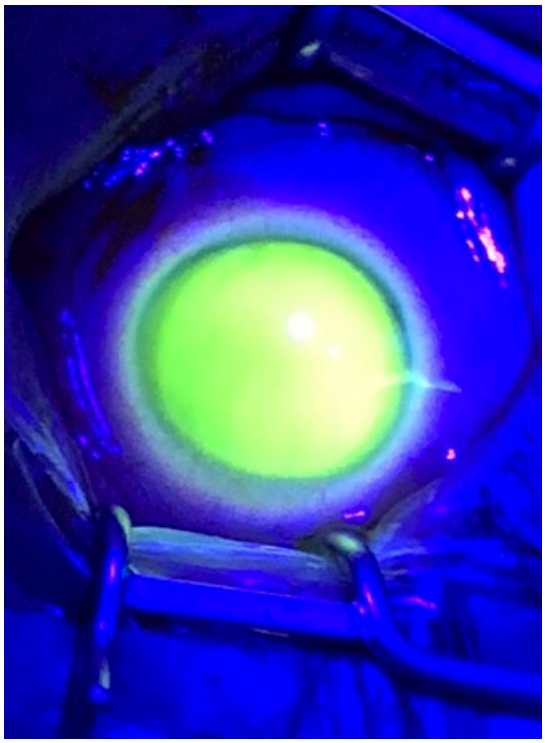
VIEW AN 8-SECOND VIDEO OF THIS CONDITION *at aao.org/eyenet, then make your diagnosis in the comments.*

LAST MONTH'S BLINK

Topotecan in the Anterior Chamber

Topotecan is a topoisomerase inhibitor that is a semisynthetic derivative of camptothecin, a plant alkaloid. It is used in treating retinoblastoma and has been successfully administered through intravenous, intra-arterial, periocular, and intravitreal routes. It fluoresces in ultraviolet light.

This child had unilateral retinoblastoma with anterior chamber seeding after primary treatment, thus was treated with intracameral topotecan. The drug (20 µg/0.05 cc) was injected into the anterior chamber with a 33-gauge needle. In this image, the entry site is visible temporally, and the drug in the anterior chamber fluoresces, as do the aqueous veins of Ascher. There was no corneal toxicity once the drug cleared.



WRITTEN BY **DAVID H. ABRAMSON, MD,** AND **JASMINE H. FRANCIS, MD.** PHOTO BY **DAVID H. ABRAMSON, MD.** DR. ABRAMSON AND DR. FRANCIS ARE AT MEMORIAL SLOAN KETTERING CANCER CENTER AND WEILL-CORNELL MEDICAL SCHOOL IN NEW YORK, N.Y.

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Michael Patterson, DO

EYE CENTERS OF TENNESSEE
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Be a Champion for Patient Safety by Supporting the Surgical Scope Fund
When high surgical standards are threatened nationwide, the Academy's Surgical Scope Fund can deliver resources, expertise and winning strategies for protecting patient safety and preserving surgery by surgeons.

Read more of Dr. Patterson's thoughts and make your confidential Surgical Scope Fund contribution at aao.org/ssf.

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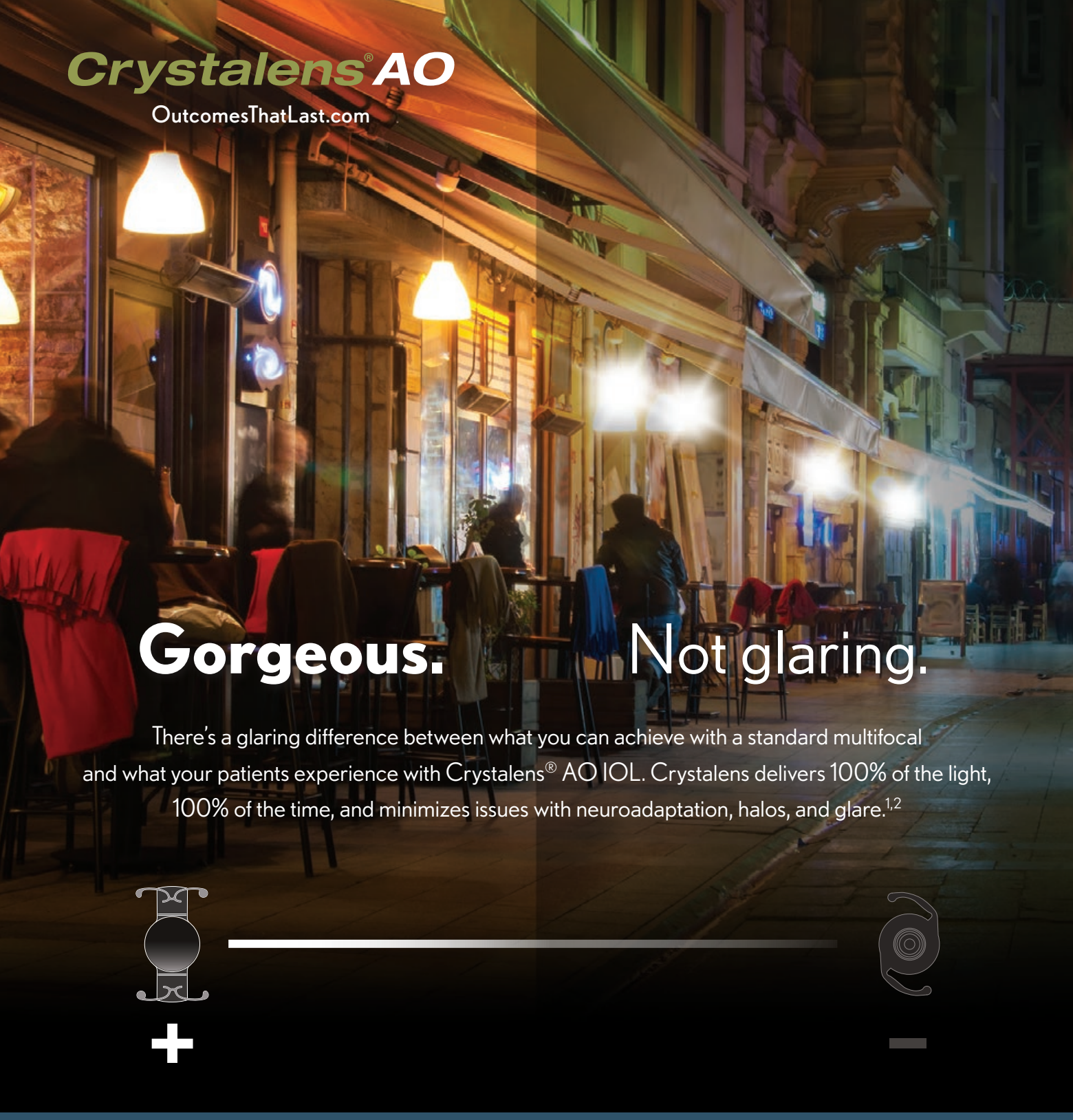

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BRIEF STATEMENT

Rx only. **Indications for Use:** The Crystalens is intended for primary implantation in the capsular bag of the eye for the visual correction of aphakia secondary to the removal of a cataractous lens in adult patients with and without presbyopia. The Crystalens provides approximately one diopter of monocular accommodation which allows for near, intermediate, and distance vision without spectacles. **Warnings:** Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient. Some adverse events which have been associated with the implantation of intraocular lenses are: hypopyon, intraocular infection, acute corneal decompensation, and secondary surgical intervention. **Precautions:** Do not resterilize; do not store over 45°C. **ATTENTION:** Refer to the Physician Labeling for complete prescribing information.

References: 1. Ang R. Comparison of 3 presbyopia-correcting IOLs used in cataract surgery. Presented at: XXIX Congress of the European Society of Cataract & Refractive Surgeons (ESCRS); September 17-21, 2011; Vienna, Austria. 2. Pepose JS, Qazi MA, Davies J, et al. Visual performance ofpatients with bilateral vs combination Crystalens, ReZoom, and ReSTOR intraocular lens implants. *Am J Ophthalmol.* 2007;144(3):347-357.