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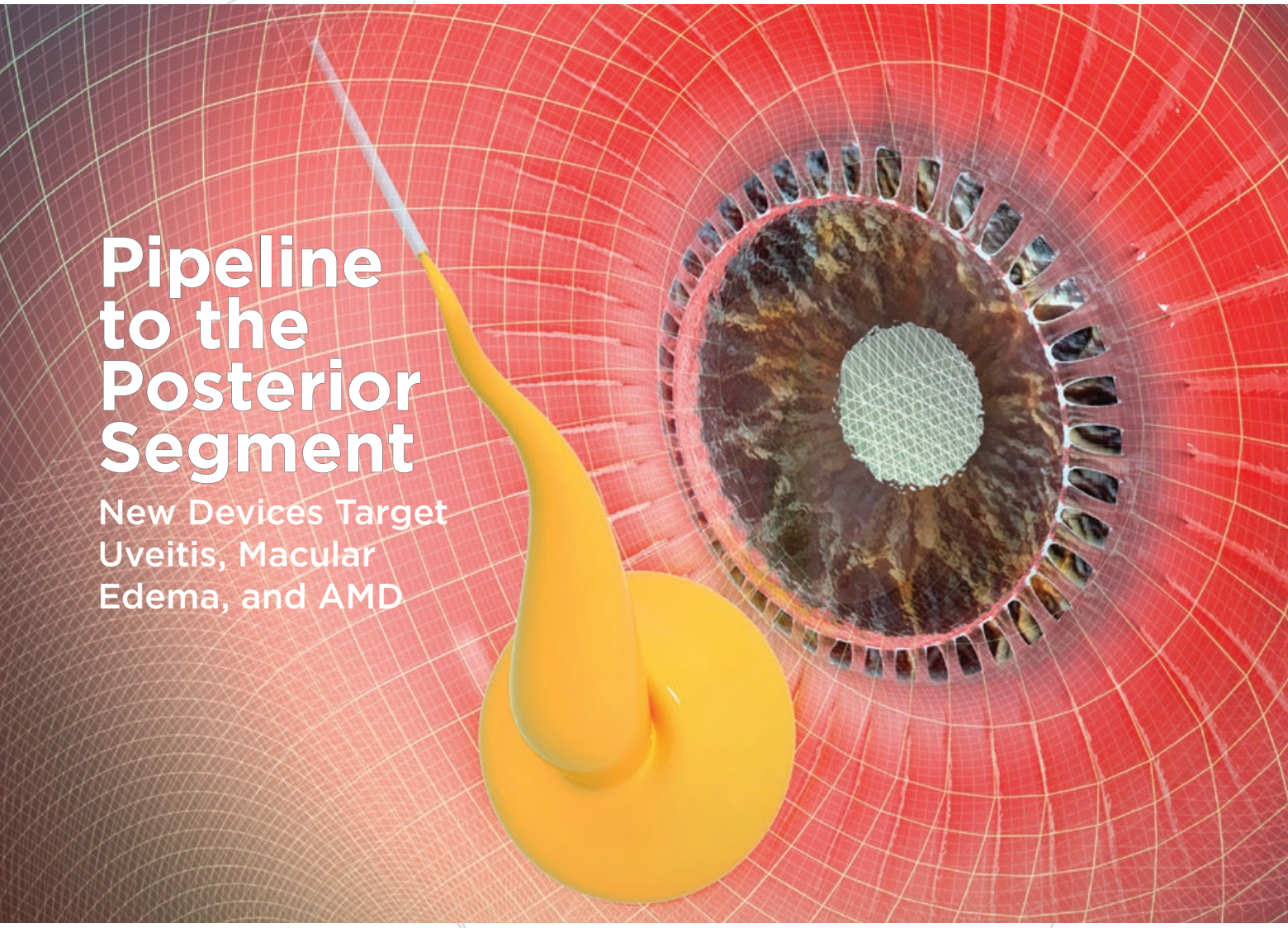

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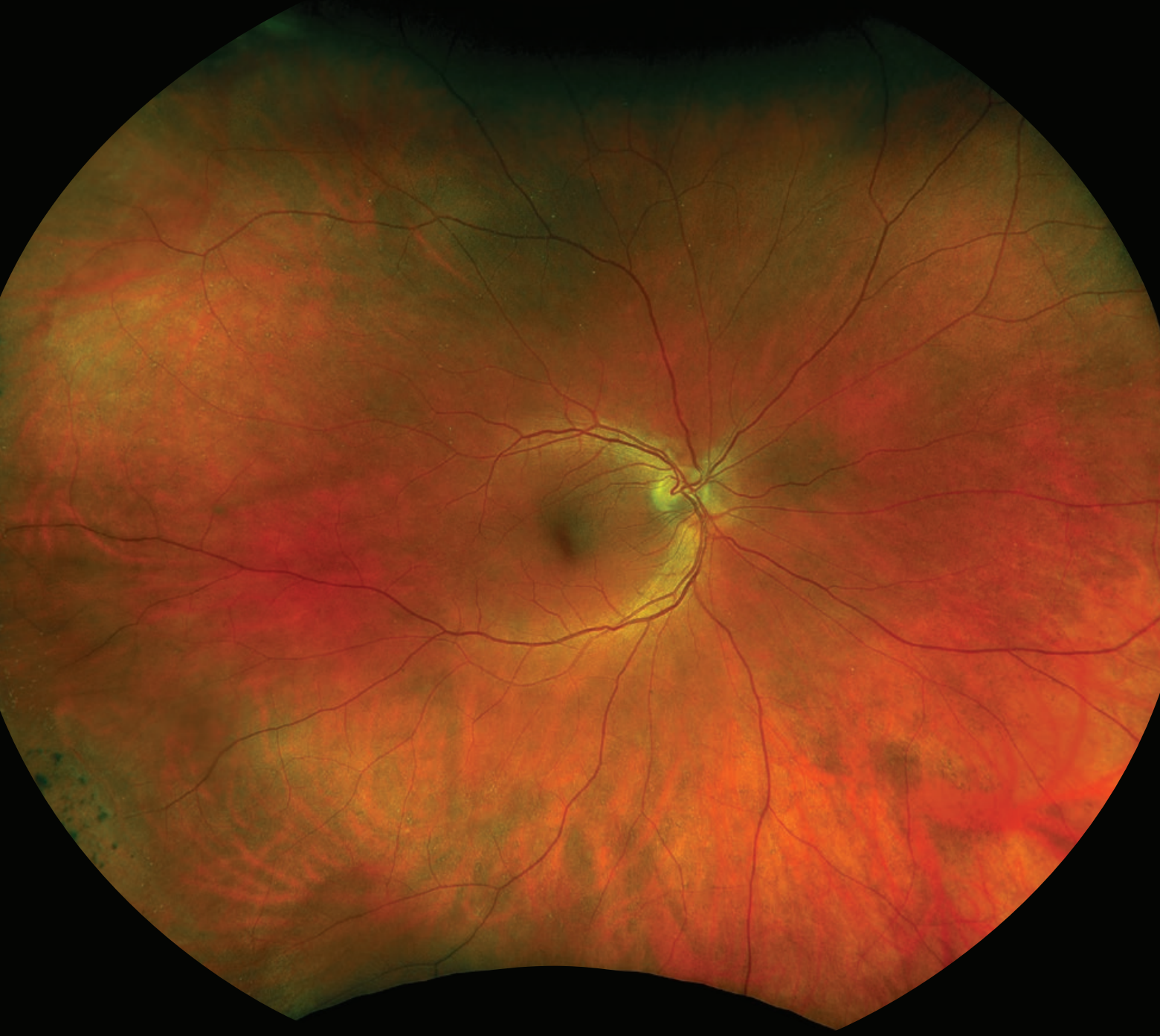

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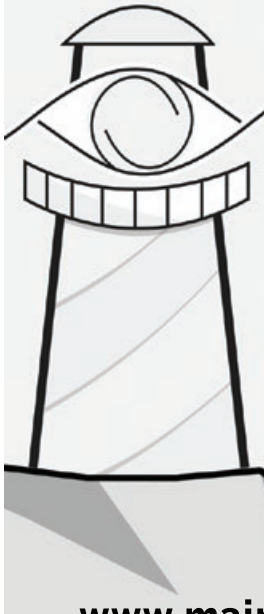

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Shirley Goggin
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Eye Physicians and Surgeons
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sgoggin@mainemed.com

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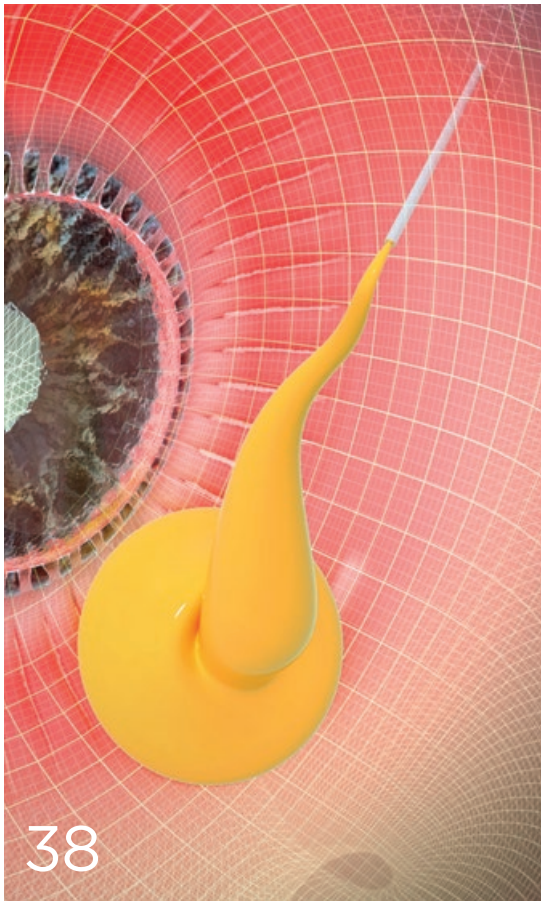

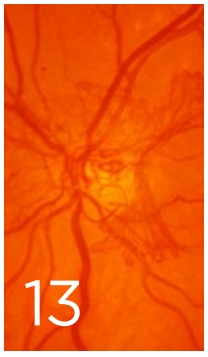

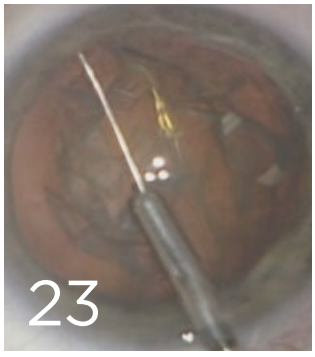

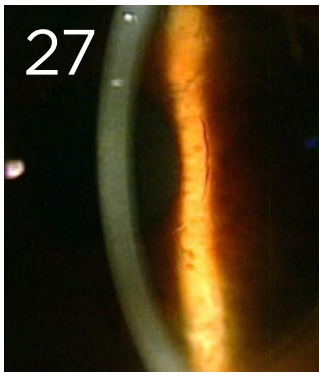

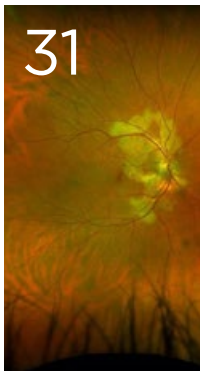

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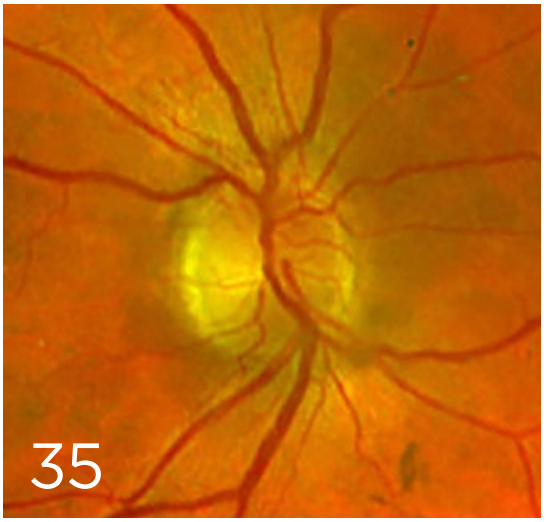

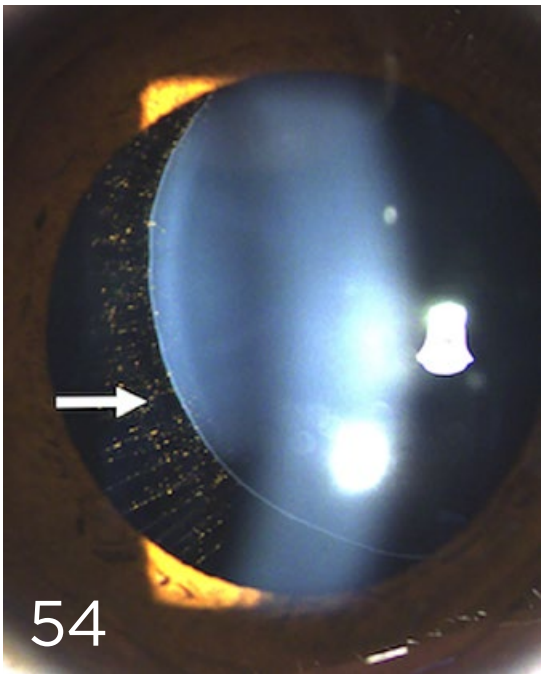

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Contributing Writers

Mark Mrvica, Kelly Miller
M.J. Mrvica Associates, Inc.
2 West Taunton Ave.,
Berlin, NJ 08009
856-768-9360
mjmrvica@mrvica.com
Advertising Sales

AMERICAN ACADEMY OF OPHTHALMOLOGY®
655 Beach St.
San Francisco, CA 94109
866-561-8558, 415-561-8500
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Letters

A Measure of Comparative Intraocular Pressure: The Glaucoma Burden Index

There is ever-intensifying interest in new glaucoma interventions, from less invasive glaucoma surgeries to alternative drug delivery systems. In assessing the efficacy of these interventions, invariably the primary outcome measure is centered on intraocular pressure (IOP), as IOP is the only modifiable risk factor for glaucoma.

Study confounders. The focus on IOP as an endpoint for studies is not without limitations. One major confounding factor is the concomitant use of medication at the time of patient enrollment and for the duration of data collection. New medications might be introduced after a specific intervention, and existing medications are sometimes tapered and stopped during the study period.

These events can confound proper evaluation of the treatment effect, and there are no agreed-upon methods to account for this, other than burdensome washout events at the start or end of a study or specifically prescribed treatment events that may not be practical during the time that the study is being conducted. Washout IOPs are also time-consuming and costly in real-world studies and are often not supported by institutional review boards due to the possibility of a participant incurring an injury to the optic nerve during periods of nontreatment.

These issues are magnified for retrospective studies in which real-world data are interpreted with inability to account for the medication effect as a whole. In addition, it may be of value to compare studies retrospectively and tease out details on how one treatment might compare to another treatment. Leveling the playing field regarding each study's use of medications would be valuable in these circumstances.

Index of IOP. If we were to combine IOP and medication use into a single measure, we might be able to eliminate a major confounding factor and provide a more objective comparison between study populations in different studies. This idea that we are proposing could be thought of as an index of comparative IOP.

In many respects, this index could represent glaucoma burden. One could state that the higher the IOP, the greater the "glaucoma burden" on any given optic nerve. Similarly, one could postulate that the greater the number of medications needed to achieve said IOP, the greater the glaucoma burden.

We are fortunate in that Jampel et al. have provided blueprints for such an index of comparative IOP.[1] Using IOP washout data from a prospective trial, they determined the effectiveness of one, two, and three glaucoma medications. When one medication was washed out, the IOP rose 5.4 mm Hg; two medications, 6.9 mm Hg; and three medications, 9.0 mm Hg.

One study examined the effect of adding a fourth medication and found that it resulted in a 3.5 mm Hg drop in IOP at 12 months.[2] However, the period studied was January through December 2000, and the most frequently added medication was a prostaglandin analog. This does not reflect current practice patterns for which a prostaglandin analog is considered first-line therapy and would rarely be the fourth agent added to a patient's regimen. We chose 1.5 mm Hg as the postulated effect of the addition of a fourth glaucoma medication. While this is somewhat arbitrary, it does reflect the authors' clinical impression of the effectiveness of a fourth glaucoma medication.

Thus, the algorithm we propose for the glaucoma burden index (GBI) is as follows:

- If number of medications is zero, GBI = IOP
- If number of medications is 1, GBI = IOP + 5.4
- If number of medications is 2, GBI = IOP + 6.9
- If number of medications is 3, GBI = IOP + 9.0
- If number of medications is 4, GBI = IOP +10.5

The literature is clear that lowering IOP slows glaucoma progression.[3] We are not proposing replacing IOP as a measure of disease risk in an individual patient. Rather, the GBI would allow assessment of comparative IOP across populations as well as objective comparisons of interventions in different clinical trials.

TABLE 1: Relationship between IOP, medication use, and glaucoma burden

IOP	Meds	GBI
15	1	20.4
15	2	21.9
15	3	24.0
15	4	25.5

As a more objective method of differentiating between new medical and surgical interventions, the GBI can help researchers, clinicians, and industry members alike. The hope would be that we would have a new tool to better guide our current understanding of available therapies as well as enhance our ability to categorize the therapeutic effects of future interventions.

Mohammed K. ElMallah, MD
Ocala, Fla.
Khaled Bahjri, MD, PhD, MPH
Loma Linda, Calif.

1 Jampel HD et al. *JAMA Ophthalmol.* 2014;132(4):390-395.
2 Neelakantan A et al. *J Glaucoma.* 2004;13(2):130-136.
3 Heijl A et al. *Arch Ophthalmol.* 2002;120(10):1268-1279.

A Response

"A Measure of Comparative Intraocular Pressure: The Glaucoma Burden Index" keenly sheds light on some of the challenges in comparing studies performed without rigorous medication washouts at baseline and last follow-up. The authors' proposed solution, a glaucoma burden index (GBI), is an interesting concept and could prove valuable in assessing the burden of medications on patients' quality of life and assessing costs related to glaucoma treatment.

While the authors' criticisms of randomized clinical trials (RCTs) do have some merit, they do not consider the fact that many seminal glaucoma RCTs in the last few decades have accounted for inclusion/exclusion criteria relatively well, and some have looked at optic nerve status or even visual fields rather than IOP alone as determinants.

In the table that the authors have proposed, an increased number of medications is associated with increased GBI. Despite the letter's attention to the confounding effects of medications on IOP, this design fails to account for the real impact on patients—in particular, further damage to the optic nerve and disease progression.

The index also fails to account for issues such as patient forgetfulness, improper eyedrop administration, and financial barriers, all of which have the potential to affect patient responses to medications (and incremental washout) in variable ways that yet unfortunately cannot be accurately measured. Furthermore, medications vary in efficacy, dosing frequency, and side effects, which is why the FDA and the American Glaucoma Society recently concluded that medication washouts should be performed at baseline and last follow-up, which is the current standard for new devices.[1]

Ahmad A. Aref, MD, MBA
Chicago
Sarwat Salim, MD, FACS
Boston

1 www.fda.gov/downloads/MedicalDevices/NewsEvents/.../UCM390327.pdf.

SHARE YOUR INPUT. Sending a letter to *EyeNet* is just one way to be heard. You also can contact your state, subspecialty, and specialized interest society's representative(s) on the Academy Council, which presents concerns to the Board of Trustees. Academy members also can attend the Oct. 13 Fall Council Meeting in San Francisco.

Find more information at aao.org/council.

Opinion

RUTH D. WILLIAMS, MD

Editorial Jiu Jitsu: Covering Innovation While Sidestepping Bias

Innovation in the ophthalmology space is accelerating. Until just a few years ago, glaucoma was treated with the same medications, lasers, and surgeries that we'd used for decades. Now there are new topical medications and an array of novel procedures to disrupt the well-worn algorithms of glaucoma care. The pipeline is in full flow.

It's no different in retina and uveitis, and—most amazing of all—gene therapy for Leber congenital amaurosis forecasts an era of treatments for genetic causes of blindness. What's more, our patients arrive with information about an emerging or expected new treatment and wonder if it's right for them. How do we digest the deluge of innovation, assess new ideas, and provide explanations to our patients?

By reading *EyeNet*, of course.

Last month's cover story was about alternatives for drug delivery in the anterior chamber; this month's addresses new drug developments for the posterior chamber. Every product discussed in these two articles either is in development or was recently approved. And here's the editorial conundrum: Many of the ophthalmologists with detailed knowledge about such products have also participated in the phase 1-3 trials.

How, then, do we discuss new and emerging products—medications, devices, or technology—when industry funds the research and the ophthalmologists we interview are the researchers? How does *EyeNet*, or any other ophthalmic publication, approach innovation?

I turned to Henry Jampel, editor-in-chief of *Ophthalmology Glaucoma,* because editors of peer-reviewed journals have an important role as gatekeepers of the scientific literature. "It's our job to assess the quality of the research and hold early series trials to a high standard," he said. Henry emphasized "the constant striving for our core value of providing unbiased evidence," which is a surprisingly challenging process. The editors and the peer reviewers analyze the studies for methodological bias—and the editors must be on the lookout for conscious or unconscious bias among the peer reviewers. Henry also noted that even when the evidence is sound, it's important that the abstract and the conclusion are consistent with the evidence. "It's particularly important to keep the abstract bias free since this is the only part of the study that many people read," he said.

Not even scientific data at the heart of a study are free of bias. In a recent editorial in *Ophthalmology*, Gerami Seitzman and Thomas Lietman pointed out the pitfalls of interpreting the data of randomized clinical trials for dry eye treatments.[1] They discussed regression to the mean, placebo effect, and the natural course of dry eye disease—and, most interestingly, clinicians' desire to "believe our actions are directly responsible for our patients' improvements." Specifically, as authors parse the data, internal motivations and beliefs can affect the analysis. Another example of unconscious bias is when physicians want to be friendly to innovation and, as Henry said, "can become echo chambers for the company." A few naysayers are important, and a "smart company will find several physicians who critically analyze the early-stage proposals," he said.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Although the challenges are different at a newsmagazine, *EyeNet* also works hard to be fair and unbiased. We often ask several experts to share their experience and perspectives on a topic. However, when we present innovative treatments, as in these two cover stories on drug delivery, the ophthalmologists who share their insights typically have financial interests related to the products under discussion. It's a tension inherent in our system of drug and device development, because industry drives this stage of research.

The cutting edge is where, arguably, the most interesting developments lie, and it's also where only those closest to the products can provide real news and valuable insight. Our goal: to approach this tension with attention to the facts, balanced questions, and full disclosure.

1 Seitzman GD, Lietman TM. *Ophthalmology*. 2019;126(2)192-194.

Current Perspective

DAVID W. PARKE II, MD

Private Equity: An Introduction

Whenever I'm speaking to a group of ophthalmologists, I can count on someone asking, "What is the Academy position on private equity [PE]?"

I always start my response by saying, "The Academy doesn't have a position on PE purchase of ophthalmology practices, but…" The "but" is that the Academy cares very much that each ophthalmologist who is considering PE has done complete due diligence and understands the economics, the nonfinancial terms, and the operational and professional implications. The Academy believes that the structure, operation, and sustainability of each member's practice is critical to her/his professional satisfaction and to the best patient care.

Occasionally, I will encounter colleagues who have entered into negotiations without understanding the fundamentals of a business relationship with a PE firm. They seem to assume that it means getting a big check followed by "business as usual." Others assume that it is exactly the same as all the Physician Practice Management (PPM) companies in the 1990s. Neither is correct. Here are a few things to consider:

PE isn't new. PE firms have been purchasing equity in physician practices for over a decade, including dermatology, dentistry, gastroenterology, urology, primary care, emergency medicine, and cardiology. We can learn a lot from their experience.

What do PE firms seek? A healthy return on their investment—ideally north of 20%. And then a sale to another investor/company in three to seven years. Particularly attractive practices are those that are poorly run, fixable, and leaving money on the table; those successful high-profile practices that can be leveraged as "platform practices"; those with revenue streams that don't depend on insurance (think cosmetic oculoplastics and refractive); and those positioned to take advantage of a growing market. What we have seen in other specialties suggests that PE interest tops out at about 20% of the practice market.

What does the upfront cash distribution represent? This is a key question. It reflects anticipated future earnings. So upfront cash will be offset downstream by PE taking a percentage of future earnings. Upfront cash is calculated as a multiple of EBITDA (earnings before interest, taxes, depreciation, and amortization) and is typically adjusted for physician compensation. It generally creates a substantive liquidity event. As the most strategically valuable practices leave the market, the multiples frequently decrease.

Will my practice run the same way with PE as a partner? It's not likely to do so. The PE company intends to grow the net income. That occurs in only a limited number of ways—increasing revenue (better payer or procedure mix, adding doctors, or simply adding patients), decreasing expenses (particularly staff), or paying you less. This may be good or bad, obviously.

What happens when the PE firm wants to sell the practice? You likely won't have any veto powers over a change in control. And the new owner/manager may do things differently than the previous owner/manager.

What ophthalmologist profile benefits the most? Generally (but not always) the senior ophthalmologist who is within five years of retirement. The early- to mid-career ophthalmologist may, however, garner more of the upfront cash as more of their future income has been sold. Future potential partners may be most economically vulnerable and less enthusiastic about joining the practice. On the other hand, if the PE firm can "grow the pie," everyone may win.

David W. Parke II, MD
Academy CEO

It's clearly a very complicated issue. Fortunately, there are many resources available to help you learn about the PE issue in much more detail—including at the upcoming AAO 2019 in San Francisco, where there will be many courses and lectures. The Academy urges every physician who is considering a PE practice equity acquisition to perform careful due diligence and seek good counsel. And, as when acquiring another practice, remember that cultural fit can be at least as important as the economics.

News in Review

COMMENTARY AND PERSPECTIVE

RETINA

Time to Rethink Glycemic Targets for Diabetes?

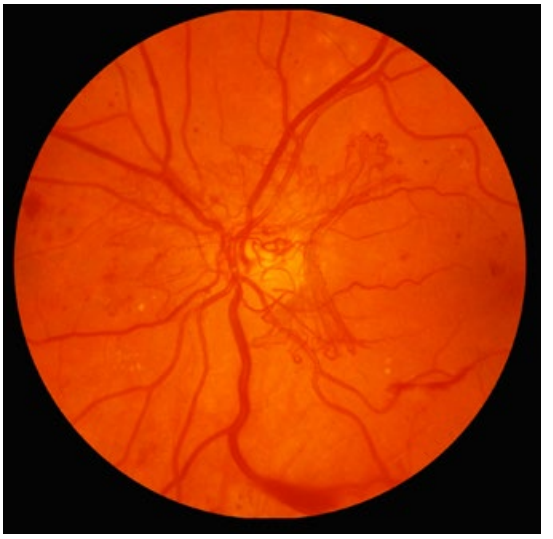
THE GLYCEMIC THRESHOLD ABOVE which diabetic retinopathy (DR) can be predicted to develop is lower for whites than it is for blacks and Hispanics, researchers have found.

In a retrospective study, a team of researchers at the University of Miami used data from 5,338 participants in the 2005-2008 National Health and Nutrition Examination Survey (NHANES). All had diabetes and had undergone digital retinal imaging to determine their retinopathy status. The analysis showed that the hemoglobin A_{1c} (HbA_{1c}) predictive threshold for the incidence of DR among white participants was 6.0%.[1] In contrast, the predictive thresholds for DR in Hispanics and blacks were 6.4% and 6.5%, respectively.

Adequate—but inadequate? "Importantly, all three race/ethnicity–specific glycemic thresholds are less than the recommended 7.0% [for optimal HbA_{1c} control] for people with diabetes," the authors wrote. "This finding suggests that adequate glycemic control does not guarantee protection from diabetic complications, such as DR."

Indeed, the researchers calculated that above these thresholds the risk of a diabetic patient developing retinopathy was approximately 4 to 6 times as high as it would be below them, said lead author Kevin J. Moore, MD, MPH, now at the University of Central Florida in Orlando.

Advising patients. Dr. Moore said the researchers hope their results will help physicians offer more individualized advice to their patients who have diabetes. "This shows that you can have individuals that are considered well-controlled for diabetes but who, based on their race or ethnicity, are still at risk for diabetic retinopathy," Dr. Moore said. "We would hope that our paper would inspire ophthalmologists and primary care providers to emphasize to patients that it's still important to follow up, regardless of how well their diabetes is controlled."



GLYCEMIC CONTROL. *Tight glycemic control in patients with diabetes is recommended as a way to prevent complications, such as the proliferative DR seen here. But should the thresholds be revisited?*

A look at the guidelines. Racial differences in mean HbA_{1c} levels have been discussed in the diabetes literature, but the reasons for these differences are poorly understood, and their potential clinical significance is unknown.[2] The American Diabetes Association (ADA) makes no recommendations that glycemic targets be modified based on race or ethnicity.[3]

Large, prospective treatment trials have demonstrated that retinopathy and other microvascular complications decrease at HbA_{1c} levels below 7.0%, and this is the appropriate target for most patients, according to the ADA's 2019 recommended standards of care.[3] However, the ADA report acknowledged, the lower complication rates achieved in studies have been accompanied by increases in the incidence of serious hypoglycemia.

Because of this risk, it would be "reasonable" for physicians to recommend a lower glycemic target of 6.5% for certain patients, if it can be met without hypoglycemia or other adverse effects, the ADA report said. This includes patients with a short duration of diabetes, long life expectancy, type 2 disease being treated with lifestyle or metformin only, or no significant cardiovascular disease.

By comparison, the Japan Diabetes Society adopted practice guidelines[4] in 2013 that endorse setting the HbA_{1c} target at 6.0% or less when the physician judges that glycemic control can be achieved through diet, exercise, or medication. The guidelines set 7.0% as the ceiling for most other patients, with the goal of preventing complications.

—Linda Roach

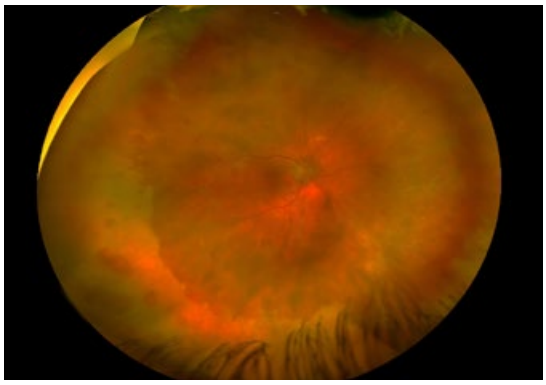
1 Moore KJ et al. *JAMA Ophthalmol.* Published online Feb. 21, 2019.
2 Selvin E. *Diabetes Care.* 2016;39(8):1462-1467.
3 American Diabetes Association. *Diabetes Care.* 2019;42(Suppl 1):S61-S70.
4 Araki E et al. *Diabetol Int.* 2016;7(4):327-330.
Relevant financial disclosures—Dr. Moore: None.

PUBLIC HEALTH

Update on Shingles Vaccine Safety

PUBLIC HEALTH OFFICIALS AND cornea specialists heralded the release of recombinant zoster vaccine (Shingrix, GlaxoSmithKline), given its ability to prevent herpes zoster (shingles) and ward off one of the disease's most serious complications, herpes zoster ophthalmicus (HZO).

The second-generation vaccine for the prevention of shingles was licensed by the FDA for adults age 50 and older in October 2017. Since then, however, the vaccine supply has been plagued with shortages, and some patients have reported side effects that prevented them from following through with the two-dose protocol.



SHINGLES RISK. *This 40-year-old woman presented with acute retinal necrosis due to HZO.*

Although the shortages are expected to persist throughout this year,[1] there is good news: According to the CDC, safety data for the eight months following FDA approval of Shingrix are consistent with comparable data from prelicensure clinical trials.[2] "Systemic and local reactions were most commonly reported, but [they] tended to be nonserious and self-limited," said lead author Elisabeth

IMAGING

Emergencies After Hours: OCT in the Eye-Only ER

OPTICAL COHERENCE TOMOGRAPHY (OCT) HAS COME out of the workday setting and into the night. Doctors at New York Eye & Ear Infirmary (NYEE) of Mount Sinai Hospital in New York report that access to OCT in the hospital's after-hours emergency eye clinic has led to timely diagnoses and vision-saving treatment. Other benefits included improved patient satisfaction and reduced physician stress.[1]

The OCT system used in this study (iScan, Optovue) is described by the manufacturer as automated; it uses computerized voice directives in multiple languages to direct patient positioning and fixation. The technical training of the NYEE ophthalmology residents took less than 30 minutes, the authors said. "Automated OCT minimizes user training, allowing the technology to slip into this acute setting seamlessly," said coauthor Richard B. Rosen, MD, at NYEE.

Review of records. Over a period of 15 months, 202 patients (359 eyes) underwent automated OCT scanning in the hospital's resident-run urgent eye care clinic. The most common complaint that prompted imaging was decreased vision (120, 59%), followed by flashes/floaters (32, 16%), then metamorphopsia, scotoma, and pain.

Impact on patient care. The imaging system proved its worth in furthering rapid triage in appropriate cases, Dr. Rosen said. For example, OCT can be helpful in diagnosing subtle cases of CRAO without characteristic fundus findings and decreased vision. One patient had increased reflectivity of the inner retinal layers and a loss of definition on OCT, confirming a suspected diagnosis of reperfused CRAO. She was transferred to Mount Sinai's main ER for a cardiovascular workup.

Impact on providers. Eighteen residents and seven fellows completed a survey about after-hours access to the imaging modality. Of the 25 participants, 21 felt that use of the automated OCT system improved patient satisfaction and reduced delayed or missed diagnoses, and 19 reported feeling less stress while using the system, as it reduced their uncertainty over subtle pathologies. "Both patients and physicians benefited by the reassurance that the correct diagnosis and appropriate triage plan could be confidently implemented in such a setting," Dr. Rosen said.

Critical caveat. This system was not effective in patients with a visual acuity of 20/400 or worse, as the device's minimum vision requirement stipulates that patients should be able to find fixation cues without operator redirection.

Bottom line. Further study may reveal the utility of automated OCT in sight-threatening conditions such as an unusual presentation of acute retinal arterial occlusion requiring interventional radiology, Dr. Rosen said. Automated OCT "in an urgent care setting can be a powerful tool for triaging a variety of sight-threatening conditions that require immediate attention," he said. The use of such a system "reduces the need to relegate this important diagnostic technology to workday settings where skilled operators are available."

—Miriam Karmel

1 Kaplan RI et al. *BMJ Open Ophthalmol.* 2019;4:e000187.
Relevant financial disclosures—Dr. Rosen: Optovue: C.

M. Hesse, MD, at the CDC in Atlanta.

Safety data. The postlicensure safety profile is based on reports to the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system. VAERS received 4,381 reports of adverse events, including reports from health care providers and the public, between October and June 2018. During that time, some 3.2 million doses of Shingrix were distributed.

Adverse reactions. Signs and symptoms included the following:

- Chills, headache, fatigue, and myalgia were commonly reported, along with injection site reactions.
- Most common signs and symptoms included fever (23.6%), injection site pain (22.5%), and injection site erythema (20.1%).
- All told, 130 (3%) of events were classified as serious.
- People between the ages of 50 and 69 reported a high percentage of systemic signs and symptoms (e.g., chills and headache). In contrast, those age 70 and older reported a high frequency of local symptoms (e.g., injection site pain).

Reassurance. Overall, Dr. Hesse said, the CDC team was "reassured" by the findings. She added that providers should expect that some patients will experience reactions to the vaccine—but that most reactions will be self-limited and should resolve in a few days. The CDC and FDA will continue to monitor the vaccine's safety profile, as the vaccine is still in the early uptake period.

Cornea risk reminder. Kathryn A. Colby, MD, PhD, at the University of Chicago, urged ophthalmologists to continue to educate patients that the vaccine is safe, effective, and can prevent HZO. "Herpes zoster ophthalmicus can cause serious cornea complications that can lead to permanent vision loss and chronic pain that impacts quality of life," she said. "It's good for ophthalmologists to educate patients on the benefit—because we're the ones who will end up managing the complications. We need to get the word out."

—Miriam Karmel

1 CDC. Current vaccine shortages & delays. www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html. Updated November 2018. Accessed March 20, 2019.

2 Hesse EM et al. *MMWR Morb Mortal Wkly Rep.* 2019;68(4):91-94.

Relevant financial disclosures—Drs. Colby and Hesse: None.

CORNEA

Lymphatic Vessels Detected in Failed Corneal Transplants

CANADIAN RESEARCHERS HAVE shown that lymphatic vessels are implicated in corneal transplant graft failure with neovascularization.[1] "Our study proves for the first time the presence of lymphatics in failed vascular corneal grafts and [shows] that they are distinct from blood vessels," said Neeru Gupta, MD, PhD, MBA, at the University of Toronto. "This work highlights the role of lymphatics in corneal transplant failure and points to a need to develop novel treatments that target lymphatic vessels to help manage the failing graft," she added.

Tissue collection. For this study, failed corneal transplant cases were selected from the Toronto Ophthalmic Pathology database. Of 273 cases, 39 contained documented neovascularization. Of these, nine cases (six men, three women) also contained suspected lymphatics. The researchers then obtained conjunctival tissue from six patients (three men, three women) with healthy corneas. These control cases were acquired from the Human Eye Biobank for Research, also located in Toronto.

Methods. The researchers selected the nine failed grafts based on results of immunohistochemistry (IHC), immunofluorescence (IF), H&E staining, and immunoperoxidase staining for CD31, a blood vessel marker. In addition, for two of these cases, they used fluorescence in situ hybridization (FISH) to detect lymphatic mRNAs, including podoplanin. All IF and FISH samples were compared with positive and negative controls and visualized by confocal microscopy.

Results. Podoplanin-immunoreactive lymphatics were detected in all nine failed grafts by IHC; of these, seven also were positive by IF. Moreover, two of the cases were positive for at least two lymphatic markers simultaneously.

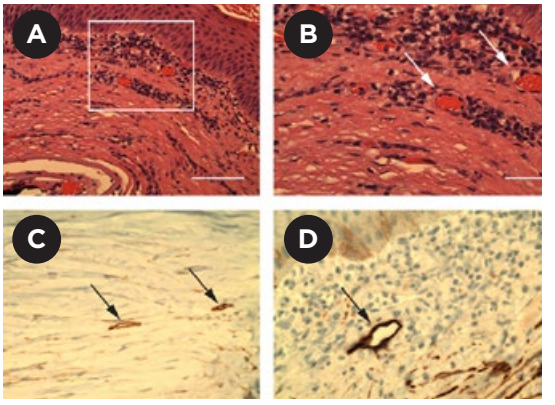
H&E stained sections of failed grafts showed mononuclear inflammatory cells at both low and high power, and neovascularization was confirmed in every case of corneal graft failure by detection of CD31-positive profiles. Varying lymphatic sizes and morphologies were seen both among separate cases and within a single case, and myriad unique lymphatic morphologies were seen.

Next steps. The researchers emphasized that their findings stress the importance of developing new tools, therapies, and imaging modalities to bring about improvements in graft survival.

—Arthur Stone

1 Diamond MA et al. *Br J Ophthalmol.* 2019; 103(3):421-427.

Relevant financial disclosures—Dr. Gupta: None.



FAILED GRAFTS. *These images show neovascularization and suspected lymphatics within failed corneal grafts. Blood vessels shown at 20× magnification (rectangular area, A) and at 40× magnification (arrows, B). Immunoperoxidase images show podoplanin-antibody staining lymphatics (arrows, C and D).*

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

Durability of DR Improvement With As-Needed Ranibizumab

May 2019

In this open-label extension of the RIDE and RISE studies, **Sun et al.** looked at the durability of improvement of diabetic retinopathy (DR) after patients were switched from monthly ranibizumab to pro re nata (PRN) dosing. They found that the DR improvements attained with monthly ranibizumab were maintained in more than 70% of patients after the switch to PRN dosing.

The extension study was a pooled analysis of data for patients with DR and diabetic macular edema (DME) who participated in RIDE or RISE for 36 months. In those studies, patients were assigned randomly (1:1:1) to receive ranibizumab 0.3 mg/month, ranibizumab 0.5 mg/month, or a monthly sham injection. After 24 months, the sham group received ranibizumab 0.5 mg/month.

After 36 months in the core studies, patients in the open-label extension (n = 500) could receive ranibizumab 0.5 mg PRN. DR severity was assessed photographically, using the scale from the Early Treatment Diabetic Retinopathy Study. The primary outcome of the extension study was the change in DR severity from months 36 to 48, according to retreatment status.

Among patients in the open-label extension, 121 (24%) did not require further ranibizumab treatment. DR was evaluable for 367 patients at months 36 and 48. When comparing all three study groups (sham/crossover, ranibizumab 0.3 mg, and ranibizumab 0.5 mg), of the 279 patients who required continuation of ranibizumab, 84% to 94% experienced stability of DR (0- to 1-step change), and 2% had improvement of 2 steps or more. However, 3% to 14% had worsening of at least 2 steps between months 36 and 48. In general, visual improvement was maintained throughout the extension study, regardless of changes in DR severity.

The authors recommend that careful monitoring be part of the long-term management of DR, particularly because the condition often worsens. They added that their findings suggest the possibility of a paradigm shift in DR treatment—that is, focusing on early treatment to reduce DR severity and prevent vision-threatening complications, rather than using a wait-and-watch approach in which treatment is reserved only for advanced eye disease. *(Also see related commentary by Robert N. Frank, MD, in the same issue.)*

Can Patient-Reported Outcomes Serve as Endpoints in Trials?

May 2019

On behalf of the United Kingdom Glaucoma Treatment Study (UKGTS) investigators, **Jones et al.** gathered and compared self-reported outcomes for UKGTS participants. In the flagship trial, patients with open-angle glaucoma (OAG) had been assigned to receive latanoprost or placebo drops, and visual field progression was the outcome of interest. Eligible for the subsequent study were patients from UKGTS with newly diagnosed OAG and self-reported outcome measures at both baseline and study completion. Because the average changes in patient-reported outcome measures (PROMs) for health- and vision-related quality of life were found to be similar for the placebo and active-treatment groups, the researchers surmised that PROMs may not be sensitive enough to function as primary endpoints in clinical trials of early-stage glaucoma.

The PROM study included 182 patients who received latanoprost and 168 placebo recipients. At baseline and trial exit, participants completed general health PROMs (European Quality of Life in 5 Dimensions [EQ-5D] and 36-item Short Form [SF-36]) as well as glaucoma-specific PROMs (15-item Glaucoma Quality of Life [GQL-15] and 9-item Glaucoma Activity Limitation [GAL-9]). The percentage change between PROM values was calculated for each patient and compared between treatment arms. Also compared were

differences between patients whose glaucoma remained stable and those who experienced progression (determined by visual field changes).

The average percentage change in PROMs was similar for the placebo and latanoprost groups, with no significant between-group difference for any measure (EQ-5D overall, p = .98; EQ-5D visual analog scale, p = .88; SF-36, p = .94; GQL-15, p = .66; GAL-9, p = .87). As expected, there were significant differences in glaucoma-related PROMs between patients with and without progressing glaucoma (GQL-15, p = .02; GAL-9, p = .02), and the differences in general health PROMs were similar for these subgroups (EQ-5D, p = .62; EQ-5D visual analog scale, p = 0.23; SF-36, p = .65).

The low sensitivity of PROMs may render these tools inadequate as primary endpoints in trials of early-stage glaucoma. Although sensitivity to clinical meaningfulness is a common criterion for outcomes selection, quality of life is important as well. Even if PROMs cannot capture the disease-modifying effects of treatment, these tools may help to assess other consequences of therapy, such as side effects and dosing convenience. *(Also see related commentary by Scott Wallace, MD, and Jane Edmond, MD, in the same issue.)*

Cyclosporine A Cationic Emulsion for Pediatric Vernal Keratoconjunctivitis

May 2019

Leonardi et al. evaluated the efficacy and safety of an investigational therapy for severe vernal keratoconjunctivitis (VKC) in children: cyclosporine A (CsA) cationic emulsion (CE). Compared with conventional CsA formulation, the new product (an oil-in-water emulsion) demonstrated better bioavailability. This research indicates that high-dose CsA CE is safe and improves keratitis, its symptoms, and quality of life (QoL) for children with severe VKC.

This phase 3 trial involved 169 pediatric patients with active severe VKC (grade 3 or 4 on the Bonini severity scale) and severe keratitis (corneal fluorescein staining score of 4 or 5 on the modified Oxford scale).

During the four-month study, patients were assigned randomly to receive high-dose treatment (CsA CE 0.1% eyedrops, four times daily), low-dose treatment (CsA CE 0.1% twice daily plus vehicle twice daily), or vehicle four times daily. The primary endpoint was a mean composite score reflecting corneal fluorescein staining, use of rescue medication (dexamethasone 0.1% four times daily), and corneal ulceration. QoL was assessed by a visual analog scale and questionnaire.

For the primary endpoint, differences in least-squares means versus vehicle were significant for the high dose of CsA CE (0.76; p = .007) as well as the low dose (0.67; p = .010); treatment effect was driven mainly by corneal fluorescein staining score. Compared with low-dose CsA CE, the higher dose resulted in larger improvements in photophobia and mucous discharge and much greater improvement in both QoL domains. The need for rescue medication differed significantly between the vehicle group and each active-treatment arm. VKC symptoms and QoL improved in all three groups, and improvement was significant for high-dose treatment versus vehicle.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Using Multicolor Imaging to Detect Polypoidal Choroidal Vasculopathy

May 2019

Multicolor imaging is a novel technology that can be used to visualize pathology in the posterior pole. Images are produced separately from three color wavelengths and can be combined to produce a composite image. **Tan et al.** evaluated the ability of multicolor imaging to discern features of polypoidal choroidal vasculopathy (PCV) and compared those results with those seen on standard color fundus photography and indocyanine green (ICG) angiography, the gold standard. They found that multicolor imaging could detect features suggestive of PCV, making it a useful noninvasive imaging option, particularly if ICG angiography is not available.

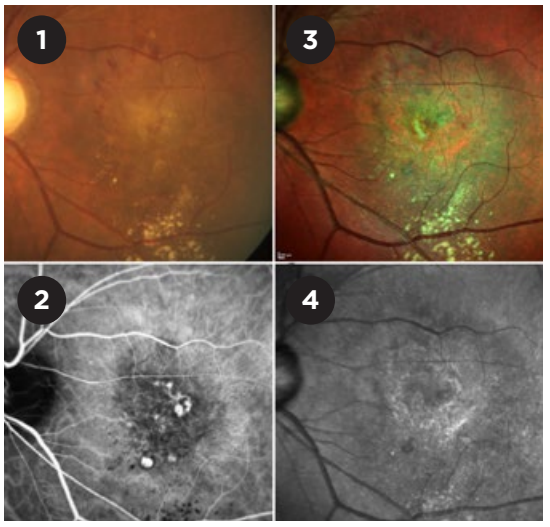
For this cross-sectional study, the researchers assessed 50 consecutive treatment-naive patients (50 eyes) with PCV. Patients were evaluated with multiple imaging technologies, including multicolor imaging, fluorescein and ICG angiography, and color fundus photography. Each patient underwent all imaging modalities on the same day. One eye was selected for analysis. The color fundus and ICG angiography images were independently graded by retina specialists to identify the presence of polyps and distinguish lesion components.

Overall, the researchers found that the location and shape of lesions detected with multicolor imaging correlated well with those seen on color fundus photography and ICG angiography. Multicolor imaging was able to detect polyps in 49 of the 50 eyes (98%). Other clinical features detected via multicolor imaging included branching vascular network (BVN, seen in 60% of eyes), drusen (seen in 66% of eyes), and subretinal hemorrhages (seen in 40% of eyes). On the multicolor composite images, the polyps appeared as dark green oval lesions. When infrared reflectance imaging was used, the polyps appeared as dark grey oval lesions with distinct margins. Subretinal hemorrhages appeared red on the multicolor composite images, while BVNs typically appeared as an area of mottling.

The authors noted that optical coherence tomography (OCT) and

Ophthalmology Retina Now in PubMed

The Academy is pleased to announce that *Ophthalmology Retina* has been accepted by the National Library of Medicine for inclusion in Medline/PubMed, making the publication the first monthly, print U.S. ophthalmology journal to be accepted in more than 12 years. Indexing is expected to begin this month (May).



PCV WITH HEMORRHAGE. *In this image set, the color fundus photograph (1) shows areas of subretinal hemorrhage with retinal edema and hard exudates. The ICG angiogram (2) illustrates polyps with a small BVN. On the multicolor composite image (3), the polyps are dark green and oval, the BVN appears as a mottled green area, and the hemorrhages are red. On the infrared reflectance image (4), the polyps appear as dark grey round lesions.*

OCT angiography were not used in this study, which opens the door to follow-up research on whether the combination of OCT and multimodal imaging would increase diagnostic accuracy. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

CRAO-Associated Vascular Ischemic Events on the Rise

April 2019

Central retinal artery occlusion (CRAO) confers a high risk of acute vascular ischemic events, including myocardial infarction (MI) and stroke. Understanding the burden and risk-factor profile of ischemic events can help ophthalmologists in managing and referring patients. **Mir et al.** performed a nationwide cross-sectional study to determine the incidence and predictors of in-hospital ischemic events among inpatients with a diagnosis of CRAO in the United States. They found that the incidence of stroke nearly doubled from 2003 to 2014. They also identified the following predictive factors: female sex, hypertension, carotid artery stenosis, aortic valve disease, smoking, and alcohol dependence/abuse.

During the 12-year study period, the estimated number of CRAO inpatient admissions was 17,117. The mean age was 68.4 years, and 53% were female. The overall incidence of in-hospital stroke and acute MI was 12.9% and 3.7%, respectively. The incidence of stroke increased significantly over time, from 7.7% in 2003 to 15.3% in 2014. Among this CRAO population, the combined risk of stroke, transient ischemic attack, and acute MI (or mortality) was 19%.

This research shows that the burden of vascular risk in this patient population is sizable and growing. At present, there are no options to significantly improve visual outcomes in patients with CRAO; therefore, clinical management involves preventing vascular ischemic events. Because stroke risk is highest at the time of occlusion, prompt clinical evaluation is warranted, along with timely execution of stroke prevention measures.

To the authors' knowledge, their study is the largest of its kind to date. The findings confirm that CRAO is an important marker for subsequent vascular ischemic events. As the incidence of CRAO-associated stroke continues to rise, it would be prudent to have an adjunctive risk-prediction model to assist in triaging and referral, the authors said. This would optimize early evaluation of patients with the highest risk for ischemic events.

New Questionnaires to Assess Functional Vision and QOL in Children With Eye Disease

April 2019

In previous research based on interviews, **Hatt et al.** identified children's concerns about functional vision and eye-related quality of life (ER-QOL). In a new study, these authors applied the patient-derived concerns to a different cohort of patients, with the goal of developing FDA-compliant questionnaires and testing their validity. This approach proved effective for devising questionnaires that separately assess the domains of functional vision and ER-QOL in children of any age, with any eye condition. (In subsequent research, the authors will test the reliability, construct validity, and responsiveness of these tools.)

The researchers' goal was to create short forms that represent individual, analysis-driven, unidimensional domains within the separate constructs of functional vision and ER-QOL, for use in any clinical setting. The researchers enrolled 444 children (0 to <18 years of age) from two centers, with the children representing 10 diagnostic categories.

Parents filled out a master questionnaire and proxy questionnaires for their children. Younger children had questions read to them; older children were given forms to fill out. Factor analysis was applied to identify unidimensional domains, and Rasch analyses (differential item functioning, targeting, fit) were performed to reduce the number of items. Rasch lookup tables were used for scoring, and the data were analyzed separately by age group and for each factor.

The number of items per questionnaire/proxy ranges from 29 to 42. The form for the youngest children (0-4 years) consists of three domains: functional vision, bothered by eyes/vision, and social. For ages 5-11 and ages 12-17, the forms include four unidimensional domains: functional vision, bothered by eyes/vision, social, and frustration/worry.

For parents, the master questionnaire includes four domains: impact on parent/family, worry about child's eye condition, worry about child's self-perception and interactions, and worry about child's visual function. The number of domains on parental proxy forms vary according to the age of the child.

Next steps include testing the reliability and validity of the new questionnaires in another cohort of patients.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Trends in Eye Care Use and Spectacle Affordability

April 2019

In an analysis of data from the U.S. National Health Interview Survey (2008-2016), **Varadaraj et al.** looked at trends in eye care use and the affordability of eyeglasses. They found that those least likely to use eye care or to be able to afford eyeglasses were women, racial/ethnic minorities, and visually impaired people, regardless of study year. Since 2014, spectacles were deemed more affordable than in previous years, which may relate to economic recovery and/or health care reform.

Survey participants were adults 18 years and older. They were grouped into nine annual cross-sectional population-based samples, ranging from 21,781 to 36,697 people. Visual impairment was defined as self-reported difficulty with seeing despite wearing eyeglasses. Outcome measures included visits to eye care professionals and the inability to afford eyeglasses if deemed needed in the preceding year. Survey logistic regression, with adjustment for demographics and other factors, was used to detect associations between survey years and eye care outcomes.

Compared with the first year of the survey, the final year was associated with higher proportions of Asians, Hispanics, and older adults in the U.S. population. Throughout the study period, substantial trends were observed for both outcomes. The fully adjusted models showed that people were less likely to use eye care in 2016 than in 2008 (odds ratio [OR], 0.90; $p < .001$). Compared with 2008, spectacle affordability was easier from 2014 onward (2014 OR, 0.82; $p < .001$; 2015 OR, 0.81; $p < .001$; 2016 OR, 0.70; $p < .001$). After adjustment for all covariates, including survey year, visually impaired people were more likely than nonimpaired individuals to use eye care (OR, 1.54; $p < .001$), but they had greater difficulty affording eyeglasses (OR, 3.86; $p < .001$). Overall, women were more likely than men to use eye care (OR, 1.42; $p < .001$) and to have difficulty affording eyeglasses (OR, 1.68; $p < .001$). Compared with non-Hispanic whites, those who are Hispanic, Asian, or black were less likely to use eye care, and Asians and blacks were more able to afford eyeglasses.

Why Children Do—and Don't—Wear Their Eyeglasses

April 2019

Nearly 13 million children worldwide have visual impairment resulting from uncorrected refractive errors. Although eyeglasses are a simple and cost-effective solution, low adherence to spectacle wear can occur in any income setting. **Morjaria et al.** looked at predictors of spectacle adherence among students aged 11 to 15 years. They found that the greatest predictors of spectacle wear were "poorer presenting visual acuity [VA]" and "greater improvement in VA with correction." The main reason for nonwear was bullying or teasing by peers. The predictors of adherence support using prescribing guidelines such as those in this study.

The study was a planned analysis of secondary objectives from a noninferiority study among students who fulfilled eligibility criteria, including correction improvement of at least 2 lines in the better eye. Participants were recruited from government schools in Bangalore, India. Masked observers documented the rate of compliance to spectacle wear during unannounced visits to the schools several months after the spectacles had been distributed.

Of the 460 participants, follow-up information was available on 362 (78.7%). At that time, 92 (25.4%) were not wearing their eyeglasses. The main reason for nonwear was teasing or bullying by peers (48.9%), followed by lost, forgotten, or stolen spectacles (26.1%). Headaches and parental disapproval also had an impact, with headaches and discomfort reported by more boys than girls (10.4% vs. 4.5%, respectively), and parental disapproval directed more at girls than boys (11.4% vs. 4.2%, respectively).

Students with poorer presenting VA and greater correction of VA were more likely to be wearing their eyeglasses: Those whose uncorrected VA was less than 6/18 (20/60) in the better eye were nearly three times more likely to be wearing their spectacles than were those whose VA ranged from less than 6/9 to 6/12 (20/30 to 20/40; adjusted odds ratio [OR], 2.84). Compared with correction resulting in improvement of 3 lines or less, correction of 3 to 6 lines was associated with an adjusted OR of 2.31, and correction of at least 6 lines had an adjusted OR of 2.57.

The fact that most students were wearing their eyeglasses at follow-up supports the use of prescribing guidelines in this study. (Spectacles are provided for students who require correction of at least 2 lines in the better eye.)

The authors emphasized the importance of interventions to reduce teasing and bullying. However, they also acknowledged that it would be difficult to address the issues underlying parental disapproval. *(Also see related commentary by Vivian Manh, OD, MS, in the same issue.)*

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Early Detection of HCQ Retinopathy With OCT

British Journal of Ophthalmology
Published online Feb. 28, 2019

Early detection of hydroxychloroquine (HCQ) retinopathy is crucial because the drug may cause severe irreversible vision loss, even after discontinuation. **Garrity et al.** evaluated optical coherence tomography (OCT) findings of patients who had taken HCQ for many years and had also undergone Humphrey visual field (VF) testing. They found that OCT was able to detect HCQ-related abnormalities before they were picked up by VF testing.

For this retrospective, observational study, the researchers identified 10

patients (17 eyes) with HCQ-related abnormalities detected on spectral-domain OCT (SD-OCT) and normal VF results. The researchers conducted several ancillary tests—including color fundus photography, fundus autofluorescence, and microperimetry—as part of a comprehensive examination.

The mean duration of treatment with HCQ was 11 years (range, 3-26 years), and the mean dose of HCQ was 1,611 g (range, 730-3,796 g). (Of note, the recommended dosage is 5 mg/kg of actual—not ideal—body weight.) At baseline, all 10 patients had visual acuity between 20/20 and 20/30 in the eye(s) with HCQ retinopathy. Three of the patients reported no visual symptoms; the remainder reported blurry vision, floaters, or photopsia.

All 10 patients presented with normal 10-2 perimetry testing. However, features of early HCQ macular toxicity were evident on SD-OCT, including attenuation of the parafoveal ellipsoid zone (relative to the central ellipsoid band) and loss of a clearly identifiable continuous parafoveal interdigitation zone. These observations were bilateral in seven patients and unilateral in three. Six eyes eventually developed advanced HCQ retinopathy with characteristic paracentral VF defects and/or advanced outer retinal disruption.

Using Deep Learning to Evaluate Macular Thickening

Investigative Ophthalmology & Visual Science
2019;60(4):852-857

Arcadu et al. set out to determine whether deep learning could be used to predict optical coherence tomography–equivalent quantitative measures of diabetic macular thickening (MT), using color fundus photographs. They found that it could, and they suggested that, when used in this manner, deep learning models could significantly benefit teleophthalmology initiatives.

For this study, the authors obtained data from the phase 3 RIDE and RISE studies of diabetic macular edema (DME); nearly 18,000 color fundus images were included. Deep learning with a transfer-learning cascade was applied to the photographs to predict time-domain optical coherence tomography (TD-OCT)–equivalent MT measures, including central subfield thickness (CST) and central foveal thickness (CFT). Two conventional TD-OCT cutoff points—250 µm and 400 µm—were used to identify abnormal MT. A deep learning regression model was created to quantify actual CST and CFT measurements from the fundus photographs. Four models of deep convolutional neural networks were analyzed (two each for CST and CFT).

The best deep learning model was able to predict CST ≥250 µm and CFT ≥250 µm, with area under the curve (AUC) of 0.97 and 0.91, respectively. For CST and CFT predictions of ≥400 µm, AUC of the best model was 0.94 and 0.96, respectively. The best neural network regression model to quantify CST and CFT had an R^2 of 0.74 and 0.54, respectively. The models were less accurate when images were of poor quality or if laser scars were present.

The researchers cautioned that their findings may not be generalizable to the overall population of patients with diabetes. In addition, it's possible that the deep learning model is not truly detecting macular thickening but rather retinal phenotypes. Although abnormal thickening does correlate with such phenotypes, the authors affirmed that the deep learning model can detect abnormal MT regardless of diabetic retinopathy severity or the presence of hard exudates. More research is needed to validate such models with real-world data. —*Summaries by Lynda Seminara*

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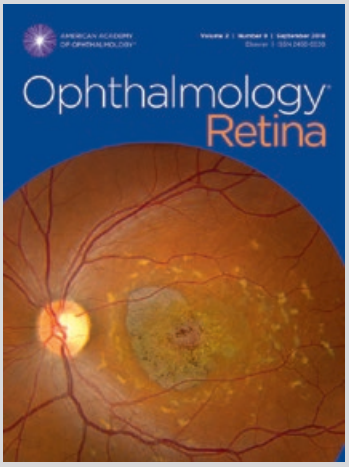

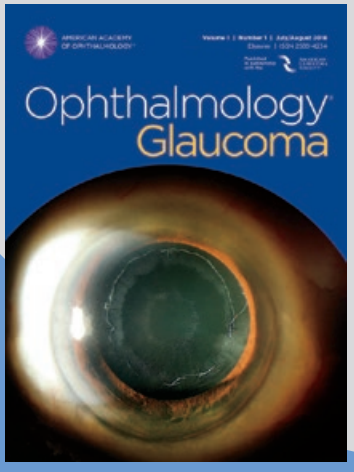

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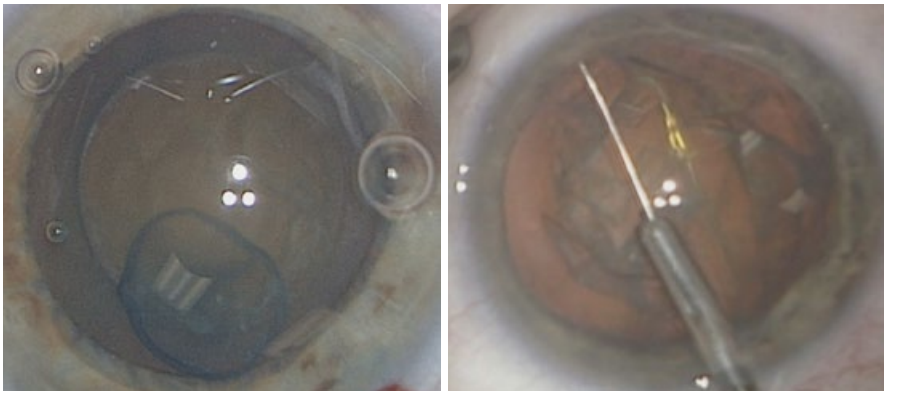
Out of Femto's Shadow: Two New Devices Seek to Change Cataract Surgery

Anterior capsulotomy and nucleus fragmentation are two of the most important steps in cataract surgery. And since its FDA approval in 2010, the femtosecond laser has introduced a way to automate these key maneuvers. However, the technology has been met with mixed reviews and uneven acceptance.

To begin with, the femtosecond laser is unavailable to many surgeons around the world. Moreover, its use requires a large outlay of capital and additional space within the surgery center or OR, adds procedural time, and results in significant extra costs. In addition, clinical studies have shown higher incidences of postoperative corneal edema and capsular tears with its use compared with manual cataract surgery.[1,2]

Enter two femto-free alternatives for facilitating capsulotomy and nucleus fragmentation: Zepto and miLoop.



CLOSER LOOK. *A Zepto capsulotomy in a mature cataract with no red reflex (left). The capsular button is stained with trypan blue and shows contracted edges. The miLoop (right) is shown encircling the nucleus with the capsular bag.*

Zepto

How it works. The Zepto (Mynosys) consists of a single-use, disposable handpiece with an elastic nitinol cutting ring at its tip. (Nitinol is a nickel-titanium alloy with superelastic and shape memory characteristics.) This tip is encased in a soft silicone suction cup. Once the cutting ring is inserted through a 2.2 mm or larger corneal incision, a pushrod is retracted, and the ring unfolds into a circular shape.

The ophthalmologist then centers the silicone cup over the visual axis and applies the necessary suction to gently draw the capsular membrane toward the ring. A 4-ms pulse of energy is delivered to the ring via a small console, instantaneously creating a complete "precision pulse capsulotomy"[3] roughly 5.2 mm in diameter, along with a free-floating capsular button.

Because the surgeon can simply replace normal capsule forceps with the Zepto during the surgical sequence, there is no disruption to the normal surgical workflow, said Joobin Hooshmand, MBBS, at the Sydney Eye Hospital in Australia.

Cost. With an initial price of $12,500 for the portable console, each single-use handpiece runs $135.

The device may be particularly attractive for ophthalmologists who want a perfectly round, reproducibly sized capsulotomy centered on the visual axis, such as when implanting premium IOLs, said Dr. Hooshmand. "For this purpose, the Zepto might be a more efficient and less expensive alternative to the femtosecond laser," commented David F. Chang, MD, in private practice in Los Altos, California.

Pearls for success. Although the device does require a surgical assistant to apply the energy and release the suctioning, "it's quite easy to incorporate into routine cataract surgery," Dr. Hooshmand said. "The learning curve is short—it takes roughly 15 to 20 cases to get comfortable."

Proper suction. In order for the Zepto to create the circular capsular opening, it's important that the surgeon achieve consistent suction on the capsule. "To do so, the central pushrod must be fully retracted all the way back to its starting position" before suction is applied, Dr. Chang said. "Otherwise,

BY MIKE MOTT, CONTRIBUTING WRITER, INTERVIEWING **DAVID F. CHANG, MD, JOOBIN HOOSHMAND, MBBS,** AND **RENGARAJ VENKATESH, MBBS.**

David F. Chang, MD

the insufficient suction could result in an uneven cut and possibly a late radial anterior capsular tear."

Dr. Hooshmand added, "If the suction cup isn't fully opened to 360 degrees, the nitinol ring won't be in the correct proximity to the capsule. But in this case, you can always disengage the suction, reapproximate the device, and then move forward."

Patient selection. The Zepto has particular benefits for complicated cases involving a poor red reflex, inadequate corneal visibility, or anterior capsular fibrotic bands, Dr. Chang said. "In my experience, there is no better technology for intumescent lens in which the liquefied cortex raises the intralenticular pressure," he said. "This is because the device cuts the entire circumference of the capsulotomy simultaneously, at once, preventing any radial splitting."

And because the Zepto bypasses the cornea altogether, Dr. Hooshmand said that he finds the device particularly useful for patients with corneal morphology or scarring that prevents good visualization of the anterior capsule.

Pupil size. In Dr. Hooshmand's experience, a dilated pupil larger than 6 mm is also necessary to achieve the best results with the Zepto. "In marginal pupils, the device tip can slip under the pupil, but bear in mind that you only get to insert the device once," he said. "So if you're in doubt regarding a patient's pupil size, take the necessary steps to enlarge the pupil beforehand."

Is it safe? "In our initial study [of Zepto], we found high incidences of incomplete capsulotomy in addition to a significant number of radial tears," said Dr. Hooshmand. "We communicated these findings to the manufacturer, and after several design improvements, a subsequent review of the device resulted in a drastic improvement in the number of complete, free-floating capsulotomies. But tear rates remained high, considerably higher than what you get with manual capsulorrhexis."[4,5]

Electron microscopy studies performed by Dr. Hooshmand and his team also revealed areas of irregular capsule margins and frayed collagen fibers at the edge of the capsulotomy button, which might be the result of dissipated thermal energy from the cutting ring.[4-6]

However, Dr. Chang explained, "Because of the way in which Zepto utilizes suction to create a capsulotomy, the button edge geometry is completely different than that of the anterior capsulotomy rim edge, which is what is important. Human cadaver studies have suggested that the rim edge is structurally smooth and strong."[3,7,8]

It remains to be seen whether or not Zepto is widely accepted, said Dr. Hooshmand. "The promise of perfect, repeatable capsulotomies is enticing," but any lingering safety concerns should be investigated, he said.

miLoop

How it works. The miLoop (Carl Zeiss) is a single-use, disposable instrument designed to mechanically fragment any grade of nucleus without the need for ultrasound energy. The device uses a retractable nitinol loop and is designed to encircle and manually bisect the lens into full-thickness segments.

"I hold the slender handpiece like a pencil," said Dr. Chang. After the capsulotomy is performed, he added, "the microfilament loop is retracted into the instrument tip and inserted into the anterior chamber via a clear-corneal incision. Advancing the sliding actuation button on the handle opens this loop in the horizontal plane, so that it expands within the capsular bag, but on top of the nucleus."

Once expanded, the loop is rotated around and behind the nucleus. The act of sliding the button backward contracts the loop and initiates the cut.

Cost. The device carries a single-use cost of $150 with no capital investment.

Pearls for success. The miLoop is particularly appealing to those ophthalmologists who are uncomfortable with chopping, said Rengaraj Venkatesh, MBBS, at the Aravind Eye Hospital in Pondicherry, India. "It eliminates the need to sculpt the nucleus and therefore the need to use ultrasonic phaco power. And because the lens is cut from periphery to center without aggressive manipulation, there is much less trauma to the capsule and the zonules."

Notes on technique. The miLoop is particularly adept at cutting through extremely dense nuclei, said Dr. Venkatesh. Even so, the surgeon must be careful not to traumatize the zonules by displacing particularly large nuclei with the loop, Dr. Chang said. "It is important to master the technique with softer and medium density nuclei before attempting brunescent cataracts."

Dr. Chang added, "The cut will tend to prolapse the distal pole of a denser nucleus. So I use a second instrument to prevent a firm nucleus from tipping and having its nasal pole prolapse through the capsulorrhexis. Many surgeons then rotate the nucleus to make a second cut 90 degrees from the first, which produces nuclear quadrants."

Patient selection. Given the miLoop's ability to cut through dense nuclei, "its use definitely benefits the surgeon working with harder and mature cataracts—especially the brunescent and black cataracts that are more common in the developing world," said Dr. Venkatesh. "The amount of phaco energy required to emulsify these cases is very high, so the miLoop provides a more efficient and beneficial alternative."

Is it safe? In a recent study of 101 patients with advanced (grades 3-4) cataracts, researchers compared outcomes in those who underwent phacoemulsification alone (n = 48) and those who underwent phaco in combination with the miLoop (n = 53). They found that the device improved overall phaco efficiency and was 100% effective in delivering ultrasound-free, full-thickness nucleus disassembly.[9] Four cases of posterior capsular tears occurred in the miLoop/phaco group, while five cases occurred in controls.

A note on humanitarian applications. Dr. Chang is part of a group convened by ianTech, the company that originally designed the miLoop, to develop a small-incision, manual extracapsular cataract extraction method using a version of the miLoop that is less expensive than the original.

The hope, Dr. Chang said, "is that a low-cost miLoop might provide a safer and more cost-effective alternative to phaco in settings where phaco training and proficiency is limited."

Game Changers?

Looking ahead, can a small box of pen-like tools such as the Zepto and miLoop truly revolutionize cataract surgery? It all comes down to affordability, Dr. Venkatesh said.

"Will there be new iterations of these devices that allow for multiple uses in multiple patients? And just how cheaply can the manufacturers deliver these products around the world? If these issues are further refined, the future is very bright for these new technologies," Dr. Venkatesh said.

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Dr. Chang is clinical professor of ophthalmology at the University of California, San Francisco, and in private practice in Los Altos, Calif. *Relevant financial disclosures: Carl Zeiss: C; ianTech: C,O; Mynosys: C,O.*

Dr. Hooshmand is an ophthalmology resident at the Sydney Eye Hospital in Sydney, Australia. *Relevant financial disclosures: None.*

Dr. Venkatesh is chief medical officer of the Aravind Eye Hospital in Pondicherry, India. *Relevant financial disclosures: None.*

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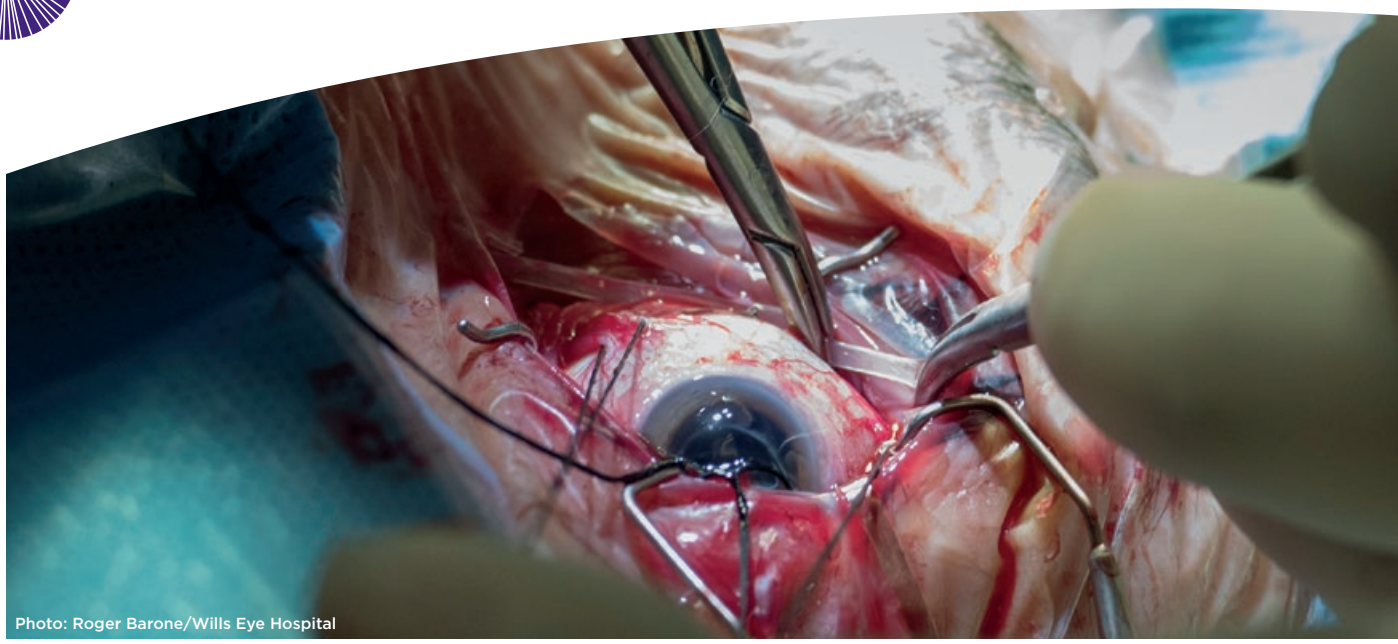

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Beyond Corneal Transplants for Fuchs: Descemet Stripping Only

Although endothelial corneal transplants generally work well, they're certainly not perfect, said Christopher J. Rapuano, MD. As it is technically challenging, "endothelial corneal transplantation may require rebubbling after a detachment or may fail altogether," he said. Accessibility of corneal tissue can be an issue; complications may include fungal infections and steroid-related glaucoma or cataracts in phakic patients; and transplants don't last forever, he added. Dr. Rapuano is at Wills Eye in Philadelphia.

"It would be great if a procedure could get the job done without using transplanted tissue," said Dr. Rapuano. Surgical removal of the Descemet membrane without subsequent endothelial transplantation—or Descemet stripping only (DSO)—may be an alternative, at least for some patients with Fuchs dystrophy.

Spontaneous Clearance

Around 2012, Kathryn A. Colby, MD, PhD, learned of case reports from Steven B. Koenig, MD, and J. Bradley Randleman, MD, showing spontaneous corneal clearance after graft detachment and after iatrogenic Descemet membrane stripping during cataract extraction.[1,2] Also catching her eye were other case series of spontaneous clearance after failed Descemet membrane endothelial keratoplasty (DMEK) in Fuchs dystrophy—but not in pseudophakic bullous keratopathy (PBK).[3]

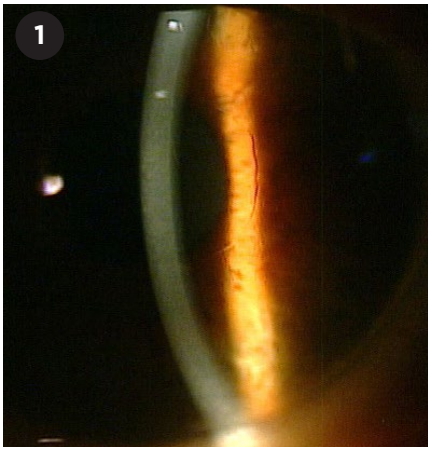
"I knew immediately this was important because it told me there was some regenerative capacity in the remaining endothelium in patients with Fuchs dystrophy but not in those with PBK," said Dr. Colby, at the University of Chicago.

She waited for the right patient and performed her first DSO. "At his one-month visit, the patient reported, 'I'm clear,'" she said. "Lo and behold, his cornea had cleared. After five years, the patient is still doing really well," said Dr. Colby, who has treated about 35 patients to date.

DSO success rates. Dr. Colby recently reviewed all DSO case series published as of 2018. She found an overall 82% corneal clearing rate in a total of 77 cases. Among other factors, patient selection, surgical protocol, or extent of disease likely influenced outcomes, she said.

In reviewing all of the published series, Dr. Colby noted a correlation between corneal clearance and size of the stripping. There's a point at which there's not enough peripheral endothelium to repopulate the central cornea, she said. One author also attributed lack of clearance to an abundant use of steroids after surgery, she said.

DSO versus DMEK. Deepinder K. Dhaliwal, MD, at the University of Pittsburgh Eye Center, recently conducted a retrospective case series comparing 12 patients who had DSO with 15 who had a DMEK.[4]



TECHNIQUE. *Slit lamp shows edge of stripped area in a DSO patient.*

"We compared the two groups to see if there were any differences in complications, final visual acuity, and time to functional visual acuity," she said. "The average time to reach a 'functional' vision of 20/40 was 2.2 weeks in the DMEK group and 7.1 weeks in the DSO group (this was statistically significant). However, the average final best pinhole visual acuity was 20/25 in DMEK eyes and 20/30 in DSO eyes and was not statistically significant."

Best Candidates for DSO

DSO will not work for pseudophakic bullous keratopathy, said Dr. Colby.

Focal guttae. "A patient has to have Fuchs dystrophy with focal guttae affecting 4 mm to 6 mm of the central cornea, but not involving the peripheral

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **KATHRYN A. COLBY, MD, PHD, DEEPINDER K. DHALIWAL, MD, LAC,** AND **CHRISTOPHER J. RAPUANO, MD.**

Kathryn A. Colby, MD, PhD

cornea," she said. "Someone with guttae from limbus to limbus will not be a good candidate. You have to be able to remove most of the guttae but still have an adequate reserve of peripheral endothelium."

Dr. Rapuano agreed that patients with mild or moderate, but very central, Fuchs dystrophy are the ideal candidates, especially if they have cataracts. "The surgeon is doing the cataract anyway and can also do the DSO and see how the patient does," said Dr. Rapuano. He noted that he has not yet had what he considered an ideal candidate, although he's offered the procedure to several patients.

One good eye. Dr. Dhaliwal also considers it important for patients to have one good eye to be considered for DSO. "If someone is marginally functional and you make their vision worse, that can be problematic," she said. "Even rapid responders have poor vision right after surgery." When she has a patient with bilateral decreased vision from Fuchs dystrophy, she does a DMEK because she wants the patient's vision to recover quickly.

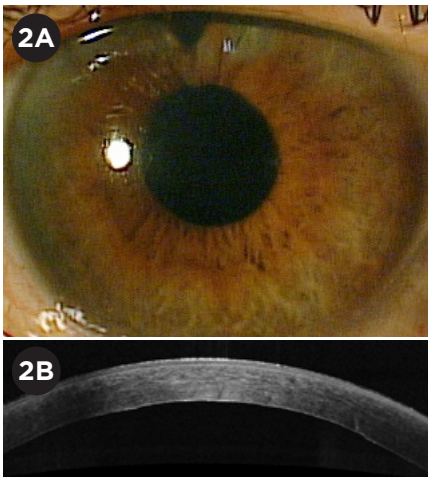
An Evolving Procedure

The DSO technique is in evolution, said Dr. Rapuano. "No one knows exactly how big a circle to take out," he said. "Some take more with success, but the more you take out, the greater the risk of failure."

Even as cornea surgeons are on a learning curve, they are taking steps to enhance the procedure.

Create smoother surfaces. Mark Gorovoy, MD, has created special forceps and refined the technique to help maximize DSO results, said Dr. Dhaliwal. "We used to score 360 degrees and then strip the membrane. Now, there's a belief we should strip in one area and tear it around using forceps. Then, endothelial cells can migrate over a smoother edge with no stromal disruption."

Dr. Colby also cited a study by Davies et al., in which 10 of 10 patients cleared when the authors used a peeling, rather than stripping, technique.[5] "Does that mean peeling is better?" asked Dr. Colby. "I don't know. My stripping technique has worked pretty well, but it does make sense that a smoother edge provides less resistance to endothelial migration."



OUTCOMES. *Five years after DSO (2A) external photograph and (2B) optical coherence tomography.*

No matter how you remove the membrane, she said, you need to use a gentle hand, avoid leaving tags of Descemet membrane, and make the cornea as smooth as possible. "In some unsuccessful cases, you can see scarring in the photos, which means the surgeon dug the Sinskey hook into the stroma during the stripping."

Consider ROCK inhibitors. "What's new since about 2016 is the adjuvant use of a topical rho kinase (ROCK) inhibitor to facilitate endothelial migration," said Dr. Colby. "Ripasudil is not FDA approved, so we can't prescribe it. But patients can order it online, and we can observe them using it."

Although netarsudil (Rhopressa) is approved in the United States for glaucoma, said Dr. Rapuano, ripasudil (Glanatec) is theoretically more effective. "At the time of the Academy's 2018 annual meeting, there were about 75 cases that had been published or presented at various meetings of supplementation with topical ripasudil after DSO," said Dr. Colby. "It appears to speed the resolution of the corneal edema and to potentially increase the final endothelial cell count."

Dr. Colby said plans are underway for a multinational clinical trial in the United States, Europe, and the United Kingdom that will assess ripasudil's effectiveness when used after DSO. Regulatory approval for the trial is in progress.

What to Expect After Surgery

Dr. Colby recommends postoperative care similar to that which follows a cataract surgery. This includes topical antibiotics for about a week after the procedure and topical steroids until corneal clearance.

Post-op patience required. "Patients have to understand that their cornea will be swollen afterward and their vision will be worse, not better, until it clears," said Dr. Colby. This could take anywhere from three weeks to three months, she said. "The length of recovery is not predictable. If you remove a larger area, however, the cornea will take longer to clear."

These patients have to be tolerant because the recovery will be a slow one, agreed Dr. Dhaliwal. "I always tell patients that their vision will get a lot worse before it gets better. If a patient is not prepared for that or not able to deal with worsened vision in one eye, DMEK is probably a better option."

Access to care. Although a cornea surgeon does the DSO procedure, said Dr. Colby, the patient doesn't need to be followed by the surgeon after the cornea has cleared. This may be beneficial for improving access to care.

When DSO Fails

Just because the cornea clears after DSO doesn't mean it will necessarily stay clear, said Dr. Dhaliwal. "In our study, all the patients did quite well. However, since we published our case series in 2018, we have already performed DMEK on one patient in that cohort, and another is showing some recurrent edema."

DMEK after DSO. The good news is there doesn't appear to be any significant risk in doing a DMEK after a failed DSO, said Dr. Rapuano. DMEK after DSO is a straightforward procedure with good results, added Dr. Colby.[6]

Don't delay. That said, it's important to not wait too long to do a DMEK after DSO. If edema is severe and long-lasting in the front of the cornea—whether from Fuchs dystrophy or after DSO—it can decrease the success rate

Kathryn A. Colby, MD, PhD

of the DMEK because there is scarring that is not removed, said Dr. Rapuano.

"When a patient's cornea stays swollen for a long time, we're doing them a great disservice because the cornea may not become totally clear again," agreed Dr. Dhaliwal. "To optimize outcomes, we need to know when to intervene surgically with DMEK." And the ophthalmologist and patient need to be on the same page about this, she said.

Potential Implications of DSO

Dr. Rapuano said he thinks that most Fuchs dystrophy patients aren't candidates for DSO given their extensive disease. However, he noted that some patients getting transplants now may have done very well if DSO had been performed earlier in the disease course.

Dr. Colby said she thinks as many as half of all Fuchs dystrophy patients may be candidates for DSO. "We know that up to 4% of people in the United States have an early form of Fuchs, which is a lot of people," she said. "If we can remove all the guttae with 4-mm stripping, put a ROCK inhibitor on for two months, and end up with a cell count of 1,000 or 1,500, I think we will be able to offer it to people earlier in the disease than would typically be done with a corneal transplant."

How long lasting? Of course, the $64,000 question is, how long will DSOs last? "We assume the cornea will get swollen at some point in the patient's life," said Dr. Rapuano. "If DSO only delays this by a year, it's not a big help. However, if it delays it by five or 10 years, that's a different story."

If the endothelial stem cell niche has truly awakened and created new endothelial cells that migrate and cover that area, said Dr. Dhaliwal, then DSO should last a long time, and it thus might even be an option for many more patients. "But if this is just a migration of existing endothelial cells, I think the jury is still out on how long it will last. We simply don't yet fully understand what is happening."

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Dr. Colby is chair of ophthalmology and visual science at the University of Chicago Medicine & Biological Sciences, in Chicago. *Relevant financial disclosures: None.*

Dr. Dhaliwal is director of refractive surgery and the cornea services, UPMC Eye Center, and a professor of ophthalmology at the University of Pittsburgh School of Medicine, in Pittsburgh. *Relevant financial disclosures: None.*

Dr. Rapuano is director of the cornea service and codirector of the refractive surgery department at Wills Eye Hospital and professor of ophthalmology at Jefferson Medical College, both in Philadelphia. *Relevant financial disclosures: None.*

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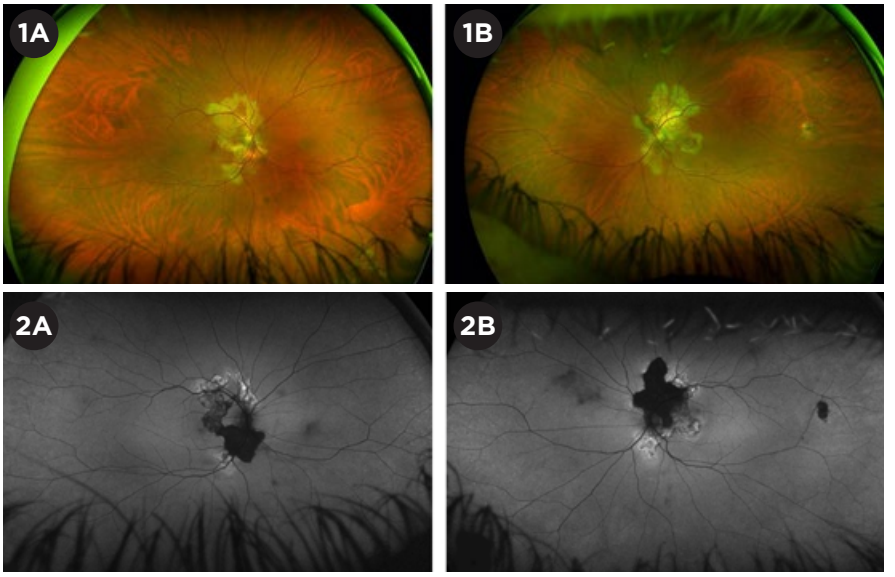
Diagnosis and Management of Serpiginous Choroiditis

Serpiginous choroiditis (SC) is a rare, bilateral, idiopathic inflammatory disorder that results in geographic destruction of the retinal pigment epithelium (RPE), retina, and choriocapillaris. It is a chronic, recurrent, and progressive disease that typically affects patients 30 to 60 years of age. There is a slight male predominance, but no racial predilection or consistent genetic factors have been associated with the disease.

Histopathologic studies have shown extensive loss of the RPE and destruction of the overlying retina. Diffuse and focal accumulation of lymphocytes has been observed in the choroid. Moreover, there is an increased frequency of HLA-B7 in patients with SC; these features are indicative of an inflammatory process.

The clinical course is characterized by multiple recurrences at intervals of months to years. Areas of reactivation are often seen adjacent to old scars. Unfortunately, patients are often asymptomatic until the fovea is involved, and they typically present with painless blurry vision and central or paracentral scotomas. Other ocular complications associated with SC include choroidal neovascularization (CNV), which occurs in up to 20% of cases, cystoid macular edema (CME), retinal vein occlusion, retinal vasculitis, and macular hole.[1,2]

There are two types of serpiginous choroiditis: classic and macular.



FUNDUS PHOTOS. *Characteristic yellow-gray geographic lesions are visible in the right eye (1A) and left eye (1B).* ***FAF.*** *Hypoautofluorescent (inactive) and hyperautofluorescent (active) lesions are present in the right eye (2A) and left eye (2B).*

Classic SC. This type comprises 80% of cases and demonstrates the characteristic bilateral asymmetric serpiginous (snakelike) or geographic yellow-gray chorioretinal lesions that typically start at the peripapillary region and can extend into the macula (Fig. 1).

Macular SC. This variant involves the macula and spares the peripapillary region. It may initially be confused with geographic atrophy, as seen in macular degeneration, or with macular ischemia associated with various vasculopathies.

Diagnosis

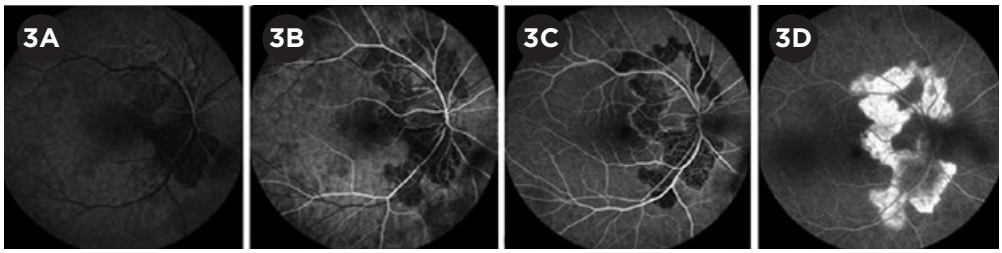
The diagnosis of SC is based primarily on clinical examination, imaging findings, and a thorough laboratory evaluation. Imaging modalities that are helpful in confirming the diagnosis include fundus autofluorescence (FAF), fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), and OCT angiography (OCTA).

FAF (Fig. 2). FAF is a very sensitive, noninvasive modality that is used to differentiate active from inactive lesions, as new lesions often occur at the border of old lesions. Acute active lesions appear hyperautofluorescent, whereas old lesions are hypoautofluorescent. Red/green wavelength ultra-

BY **AMELIA M. TODD, MD, NILOOFAR PIRI, MD,** AND **DENIS JUSUFBEGOVIC, MD.** EDITED BY INGRID U. SCOTT, MD, MPH, AND SHARON FEKRAT, MD.

widefield FAF imaging is considered the best modality to monitor disease activity.

FA (Fig. 3). Acute lesions appear hypofluorescent, with irregular and poorly defined borders in early phases of the study. This appearance is likely due to hypoperfusion of the choriocapillaris and blocked fluorescence from edematous RPE and outer retina. In the later phases, hyperfluorescent borders are seen, representing leakage of fluorescein from the surrounding intact choriocapillaris. Inactive lesions are hypofluorescent with sharp borders in early phases of the study and become progressively hyperfluorescent with variable levels of staining.

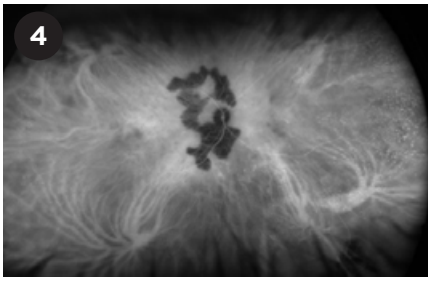


FA PHASES. *Fluorescein angiography, right eye. (3A) Early arterial, (3B) arterial, (3C) arteriovenous, and (3D) late phases. (See text for description of findings.)*

ICGA (Fig. 4). Lesions appear hypofluorescent on ICGA throughout all phases of the study, representing disruption in choroidal perfusion. Early subclinical lesions may be better appreciated on ICGA than on funduscopic examination or FA, and they may appear as hypofluorescent spots resulting from isolated choriocapillaris involvement. ICGA may also be useful in differentiating active new lesions, which are hypofluorescent, from CNV, which appears hyperfluorescent during the middle to late phases of the study.

OCT (Fig. 5). Acute lesions primarily affect the outer retinal layers and choriocapillaris and appear as increased reflectivity localized to the outer retina and disruption of the photoreceptor bands. OCT of older lesions demonstrates outer retinal atrophy and RPE disruption.

OCTA. OCTA is a newer, noninvasive method of imaging retinal and choroidal vascular anatomy that can be useful in assessing SC progression. Choriocapillaris flow disruption is an early sign of the disease, preceding structural involvement of the outer retinal layers. Prompt treatment at this early stage may allow for resolution without chorioretinal scarring.[3]



ICGA. *Late-phase ICGA of the right eye shows persistent hypofluorescence of the lesions.*

Masquerading Conditions

Before treatment for SC is initiated, an extensive workup is needed to rule out other inflammatory or infectious etiologies that may mimic the disease. The differential diagnosis for SC includes other inflammatory processes such as acute posterior multifocal placoid pigment epitheliopathy (APMPPE), ampiginous choroiditis, multifocal chorioretinitis, and persistent placoid maculopathy; infectious etiologies such as tuberculosis (TB), herpesvirus, toxoplasmosis, and syphilis; autoimmune diseases such as sarcoidosis; vascular diseases that cause retinal ischemia; and degenerative changes, such as age-related macular degeneration.

Laboratory testing for sarcoidosis, syphilis, herpes, toxoplasmosis, and TB should be part of the routine workup. If testing is negative and all diagnostic tests confirm idiopathic SC, treatment should be started promptly.[1,2]

Mycobacterium tuberculosis. This bacterium can cause serpiginous-like choroiditis (SLC). It is important to differentiate SLC from SC, as their treatments differ. Patients with SLC often present with multifocal lesions involving the periphery rather than peripapillary region. Anterior chamber cellular reaction and vitritis are also more common in SLC compared to SC. FAF may be helpful in distinguishing the two disease entities, as SC has a homogeneous hypoautofluorescent pattern, whereas SLC often demonstrates a more stippled appearance.

Both diseases are treated with oral steroids, but antitubercular medications are extremely important in treating SLC. Testing for TB with labs and a chest x-ray prior to initiating steroids is critical, as steroids may worsen SLC if used without concomitant antitubercular therapy.[2]

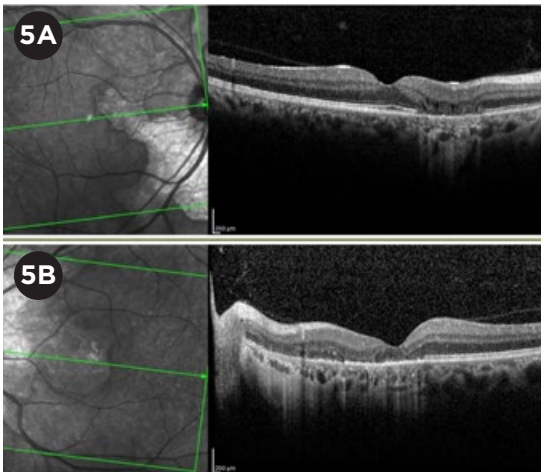
APMPPE and relentless placoid chorioretinitis (RPS). These two clinical entities can present a diagnostic challenge and may mimic SC or one another early in the course of disease.

APMPPE. Acute APMPPE lesions clinically appear similar to active SC or RPS lesions as deep yellow-gray patches at the level of the outer retina and inner choroid. They are typically multiple, discrete, and plaquelike in appearance and predominantly involve the posterior pole.

APMPPE lesions usually resolve on their own in a few weeks without treatment, with residual mild to moderate RPE changes. New lesions can develop over several subsequent weeks. Recurrent disease is uncommon and usually appears as new multifocal patches not associated with previously healed lesions. CNV is very rare in APMPPE.

RPS (also known as ampiginous choroiditis). The clinical appearance of acute RPS lesions is similar to APMPPE. However, RPS results in recurrent and progressive destruction of the choroid and retina. Lesions are usually widespread and may involve both the posterior pole and periphery. The clinical course and multifocal appearance of the RPS lesions distinguish it from SC, whereas the relentless progression of the disease differentiates it from APMPPE.[2] Treatment of RPS is similar to that of SC.

Denis Jusufbegovic, MD



OCT. *Imaging of the right eye (5A) and left eye (5B) shows complete RPE and outer retinal atrophy with subfoveal involvement in the left eye.*

Denis Jusufbegovic, MD

Management

Initial therapy for SC includes systemic corticosteroids to treat active lesions as well as concurrent immunosuppressive therapy to prevent recurrences. Oral corticosteroids are the mainstay of treatment for acute disease, but some studies have also shown that immediate intravitreal steroids may be beneficial in patients with foveal lesions.[2]

Triple therapy, including prednisone, cyclosporine, and azathioprine, has been found effective in controlling SC.[4] Monotherapy with mycophenolate mofetil, azathioprine, or cyclophosphamide has shown some success, as described in several case reports.[2]

Biologic therapy with a tumor necrosis factor α (TNF-α) inhibitor such as adalimumab has been found effective in patients who progressed despite therapy with other immunosuppressants.[5] Now, adalimumab is also frequently used as a first-line agent for SC. It is imperative to rule out TB before starting a TNF-α agent.

A recent study found that treatment with chlorambucil over six to nine months was effective in preventing recurrence and maintaining vision in 17 patients with SC. Of these, 12 patients had an average of 45 months of drug-free remission, and 14 maintained visual acuity within two Snellen lines.[6]

Complications of SC should also be addressed promptly (e.g., with anti-VEGF agents for CNV or intravitreal corticosteroids for CME).

Prognosis. Overall prognosis for this disease is poor despite treatment. Final visual acuity is <20/200 in about 25% of treated cases.[7]

Key Points

Serpiginous choroiditis is a rare bilateral, idiopathic inflammatory disorder that causes geographic destruction of the retina and choroid in healthy middle-aged individuals. This chronic, recurrent, progressive disease has a poor visual prognosis if the fovea is involved. Symptoms include blurred vision and central and paracentral scotomas. A thorough workup is necessary prior to initiating treatment to exclude other inflammatory or infectious etiologies that may mimic SC. Treatment includes corticosteroids and immunosuppressive therapy. Patients should be monitored closely for disease progression and complications, including CNV and CME.

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Dr. Todd is a second-year ophthalmology resident, and **Dr. Jusufbegovic** is an assistant professor of clinical ophthalmology; both are at the Eugene and Marilyn Glick Eye Institute, Indiana University School of Medicine, Indianapolis. **Dr. Piri** is a third-year ophthalmology resident at the Department of Ophthalmology and Visual Sciences, University of Louisville, Kentucky. *Financial disclosures: None.*

EXTRA **MORE ONLINE.** For a case report and additional images, see this article at aao.org/eyenet.

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The Case of the Blind Bibliophile

Lee Berry* was a distraught 64-year-old bibliophile who could no longer read. Six months prior to seeing us, she had experienced a rapid decline in vision, lasting one month, in both eyes. Over the next five months, a continuing, more gradual deterioration made her daily activities, such as reading and grocery shopping, increasingly difficult and, ultimately, impossible.

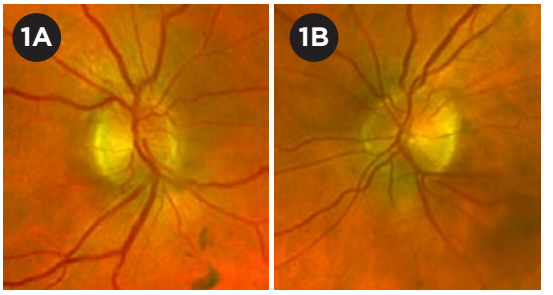
Initial testing. Perplexed by Ms. Berry's normal eye exam, several eye care providers coordinated a thorough diagnostic workup. Her medical record indicated normal or unremarkable results for the following imaging studies: magnetic resonance imaging (MRI) of the brain and orbits with and without contrast, optical coherence tomography (OCT) of the macula and peripapillary retinal nerve fiber layer (RNFL), and fluorescein angiography.

Concern for possible occult cancer and cancer-associated retinopathy (CAR) prompted computed tomography (CT) scans of the chest, abdomen, and pelvis. The latter showed only a few borderline enlarged mediastinal lymph nodes.

During the search for an answer, Ms. Berry underwent bilateral blepharoplasty for potentially vision-obstructing dermatochalasis and cataract surgery in the right eye. Neither procedure improved her vision. She was referred to us for a neuro-ophthalmologist's opinion.

We Get a Look

Ms. Berry told us that her central vision seemed worse than her peripheral vision, and she reported no associated pain or photopsias. Her medical history was notable for hypertension, coronary artery disease, dyslipidemia, depression, and anxiety. Surgical history included a cholecystectomy and a remote hysterectomy for benign fibroids. Her medications included buproprion, fluoxetine, clopidogrel, spironolactone, atorvastatin, and metoprolol. She admitted to drinking two vodka cocktails and smoking half of a pack of cigarettes daily for the past 40 years. She also reported an affinity for junk food but denied any restrictive dietary practices or eating disorders. Her family history was significant for a deceased maternal uncle who had ill-defined vision problems.



FUNDUS. *Color fundus photos demonstrating mild temporal optic nerve pallor bilaterally in the right eye (1A) and left eye (1B).*

Testing. On examination, her best-corrected visual acuity was counting fingers at 3 feet in both eyes. Her pupils were isocoric, with sluggish reactivity to light and no afferent pupillary defect. The remainder of the cranial nerve exam was unremarkable. She failed to recognize any of the Ishihara color plates in either eye, including the control plate. Her ocular motility, peripheral visual fields to confrontation (finger counting in each quadrant), and intraocular pressures were normal bilaterally.

Her slit-lamp exam was notable for a posterior chamber IOL in good location in the right eye, and a 1 to 2+ nuclear sclerotic cataract in the left eye.

The funduscopic exam was normal in both eyes, apart from mild bilateral temporal optic nerve pallor (Fig. 1).

Automated static perimetry (size V, 30-2) demonstrated similar findings in both eyes: global depression on the total deviation plot and cecocentral scotomas on the pattern deviation plots (Fig. 2).

Spectral-domain OCT (SD-OCT) of the peripapillary RNFL revealed normal thickness in both eyes (Fig. 3). Macular sections were grossly normal in the right eye, and a subtle epiretinal membrane was seen in the left eye. Fundus autofluorescence was unremarkable.

A full-field electroretinogram was essentially normal in both eyes. There was a normal cone response in both eyes, which was not consistent with CAR.

BY **COLTEN WENDEL, MD, MICHAEL S. LEE, MD,** AND **COLLIN M. MCCLELLAND, MD.** EDITED BY STEVEN J. GEDDE, MD.

Differential Diagnosis

In the context of Ms. Berry's bilateral cecocentral visual field defects and normal macular exam, our differential diagnosis included both optic neuropathies and occult retinopathies.

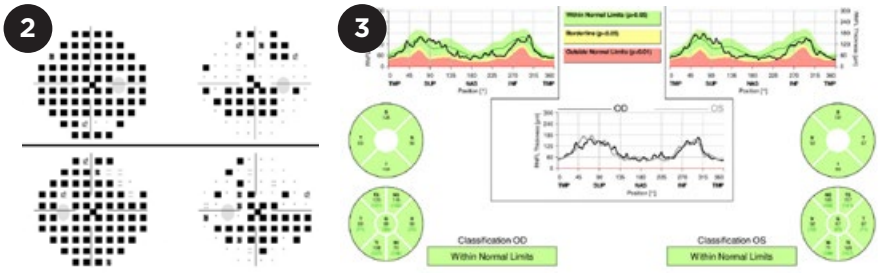
Retinal etiologies to consider included CAR, autoimmune retinopathy, or one of the enlarged blind spot syndromes (e.g., acute zonal occult outer retinopathy, multiple evanescent white dot syndrome, idiopathic big blind spot syndrome, etc.).

Narrowing the possibilities. While Ms. Berry had risk factors for occult malignancy such as her age, smoking, and drinking, she denied photopsias typical of CAR and had a negative body CT. Autoimmune retinopathy and occult CAR were essentially excluded with a normal ERG. She lacked typical clinical features of the big blind spot syndromes, including outer retinal disruption on SD-OCT, extensive enlarged blind spots on automated perimetry, photopsias, and acute-onset nonprogressive vision loss.

Organic vision loss. The presence of mild temporal optic nerve pallor, cecocentral scotomas, and sluggish pupils made it clear that there was organic vision loss and indicated the possibility of bilateral optic neuropathies. Bilateral optic neuropathy from chiasmal compression (e.g., meningiomas, pituitary adenomas, craniopharyngiomas) is relatively common but typically demonstrates a bitemporal pattern of visual field loss and is visible on a good quality MRI. Similarly, optic neuritis can be bilateral and cause any pattern of visual field loss, but it is usually painful, occurs in patients younger than 50, is rarely progressive for six months, and should be visible on MRI with dedicated orbital sequences.

Further options. Nonarteritic anterior ischemic optic neuropathy (NAION) is characterized by acute painless vision loss with associated optic disc edema at the time of vision loss, nerve fiber layer type visual field defects, and marked atrophy within several months of vision loss. Vision loss progression beyond the first month is highly atypical in NAION.

Mitochondrial optic neuropathies are marked by bilateral, often symmetric, cecocentral visual field loss, dyschromatopsia, and acuity loss. Depending on the cause of mitochondrial failure, the rate of vision loss varies from rapid (Leber hereditary optic neuropathy [LHON]) to subacute (ethambutol toxicity, thiamine deficiency) to chronic (most nutritional optic neuropathies).



TESTS. *(2) Low vision protocol 30-2 automated static perimetry demonstrating global depression in the right eye (top left) and left eye (bottom left) on total deviation plot and a cecocentral scotoma in the right eye (top right) and left eye (bottom right) on pattern deviation plot. (3) SD-OCT of the optic nerve showing normal RNFL bilaterally as compared to age-matched controls.*

Diagnosis

Although the SD-OCT showed normal peripapillary RNFL, which could point away from a diagnosis of optic neuropathy, we looked at the segmentation of retinal layers, which allowed quantification of macular ganglion cell layer (GCL) thickness. Compared with the normative data published in the literature among similarly aged Caucasians (Fig. 4A), Ms. Berry's GCL was diffusely and severely thinned bilaterally[1] (Fig. 4B), which pointed us back to an occult optic neuropathy diagnosis. The prominent discordance between GCL thinning and normal RNFL in the presence of rapid-onset central vision loss is a characteristic feature of LHON. Given this information, we ordered mitochondrial point mutation testing for Ms. Berry, which revealed a pathogenic 11778G>A homoplasmic mutation.

Discussion

LHON is a prototypical inherited mitochondrial optic neuropathy, characteristically presenting with sequential or simultaneous bilateral painless central vision loss in young men. Among those who harbor a pathogenic LHON mutation, males are up to nine times more likely to manifest with vision loss, while females tend to remain asymptomatic carriers.[2]

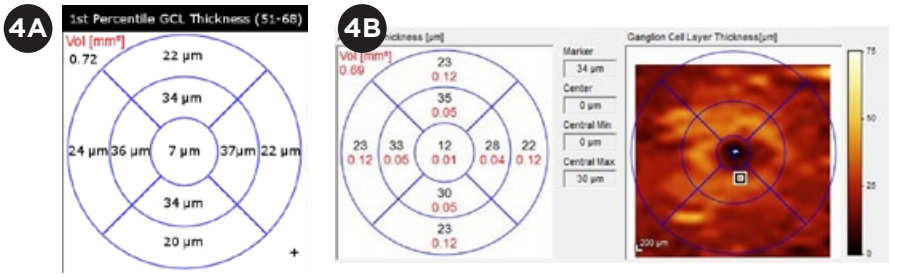
Mutations. Three primary mtDNA point mutations constitute approximately 90% of LHON cases: 11778G>A, 14484T>C, and 3460G>A. The 11778G>A point mutation is the most common in North America and the least likely to show late spontaneous visual recovery compared with the other LHON mutations.

Pathophysiology. Retinal ganglion cells (RGCs) within the papillomacular bundle are selectively affected early in LHON, accounting for the disease's characteristic visual acuity loss, dyschromatopsia, and dense central or cecocentral scotoma. While the underlying pathophysiology remains incompletely defined, it is thought that the small caliber of papillomacular bundle RGC axons makes them more vulnerable to reactive oxygen species and oxidative phosphorylation energy impairment related to mitochondrial dysfunction.[3]

In addition, individual patient factors, including poor nutrition, smoking, and excessive alcohol consumption, may contribute to mitochondrial damage and visual loss.

Signs and symptoms. At the time of acute loss of vision, the optic nerves usually appear normal but may demonstrate mild peripapillary telangiectasias and pseudoedema, which slowly changes to pallor. Similarly, over a variable period of months, OCT shows a transition from either normal or

Collin M. McClelland, MD



SEGMENTATION DATA. *(4A) Diagram displaying the first percentile normative values of GCL thickness per macular region in Caucasians aged 51 to 68 years based upon published data.[1] (4B) The patient's right eye segmentation data from SD-OCT of the macula displaying the volume and average thickness of the GCL corresponding to each macular region.*

mildly thickened RNFL to thin RNFL. A longitudinal study using high resolution OCT imaging of patients with LHON revealed that thinning of the temporal peripapillary nerve fiber layer typically occurs within three months of the onset of visual loss.[4] Pathological thinning within the macular RGC layer occurs within weeks of onset of vision loss and can even be seen as an early sign of impending vision loss during the presymptomatic phase in patients with LHON mutations. Ms. Berry's normal-thickness RNFL after six months of visual loss was uncharacteristic for LHON and made the diagnosis particularly challenging.

To recap, Ms. Berry's bilateral, severe central vision loss with sparing of the peripheral fields, mild temporal optic nerve head pallor disproportionate to her degree of vision loss, lack of a structural cause for optic neuropathy on MRI, and prominent GCL thinning on OCT segmentation of the macula in the setting of normal RNFL thickness cumulatively implicated LHON. Thus, LHON should be considered in the appropriate clinical context, even among patients who do not fit the typical LHON demographic.

Treatment

There is currently no evidence-based, effective treatment for LHON. Idebenone (a ubiquinone [coenzyme Q10] analog) holds promise for patients with early LHON but is not approved by the FDA. However, several clinical trials are underway to evaluate the efficacy of idebenone, as well as gene therapies, for LHON (see www.clinicaltrials.gov). Ms. Berry enrolled in a multicenter randomized controlled trial of idebenone treatment for LHON.

In LHON patients, it is important to identify and treat any concomitant medical conditions or habits that could contribute synergistically to impairment of mitochondrial function. Among these are poor nutrition and vitamin deficiencies (vitamin B12, thiamine, folate, copper), smoking, and alcohol abuse. These factors may be associated with expression of vision loss among carriers of Leber mutations and/or lead to further progression of vision loss after onset of LHON if not addressed. Ms. Berry's vitamin testing was normal. She was advised to stop smoking and limit alcohol consumption.

Genetic Counseling

Ms. Berry was referred to a genetic counselor for a detailed family pedigree and discussion of risks of vision loss in family members. She had two daughters who were obligate carriers of her homoplasmic LHON mutation, and several of her male grandchildren were carriers. Because they would be at greatest risk for expression of vision loss, all carriers were advised to avoid malnutrition, smoking, and heavy alcohol use for life. The ill-defined vision loss Ms. Berry described in her maternal uncle might have been attributable to LHON. Most patients with LHON (approximately 60%) are aware of a family history of vision loss compatible with the disease.

Conclusion

Clinical features suggestive of LHON include bilateral (sequential or simultaneous), progressive, and painless central visual loss with subtle or no optic nerve findings early. Although LHON is most commonly seen in males aged 10 to 30 years, it can also occur in women and can present at later stages of life. In individuals with unexplained bilateral vision loss of less than three to six months in duration, an OCT demonstrating normal peripapillary RNFL may not be sufficient to exclude optic neuropathy from LHON. A macular segmentation analysis demonstrating thinning of the GCL out of proportion to RNFL thinning can facilitate early diagnosis. Patients can then be educated to optimize their nutritional status and to minimize behaviors that are toxic to mitochondria; beyond that, they may consider enrolling in randomized controlled trials of promising experimental therapies being conducted at large academic centers.

*Patient name is fictitious.

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Dr. Wendel is a fourth-year resident at the Department of Ophthalmology and Visual Sciences at the University of British Columbia in Vancouver. **Dr. Lee** is professor and **Dr. McClelland** is associate professor of neuro-ophthalmology; both are with the Department of Ophthalmology and Visual Neurosciences at the University of Minnesota in Minneapolis. *Financial disclosures—Dr. Lee: EvolveMD: L; NEI: S; Quark: S; Springer: P; UpToDate: P; Vindico: L. Dr. McClelland and Dr. Wendel: None.*

See the disclosure key, page 8.

Write a Morning Rounds Article

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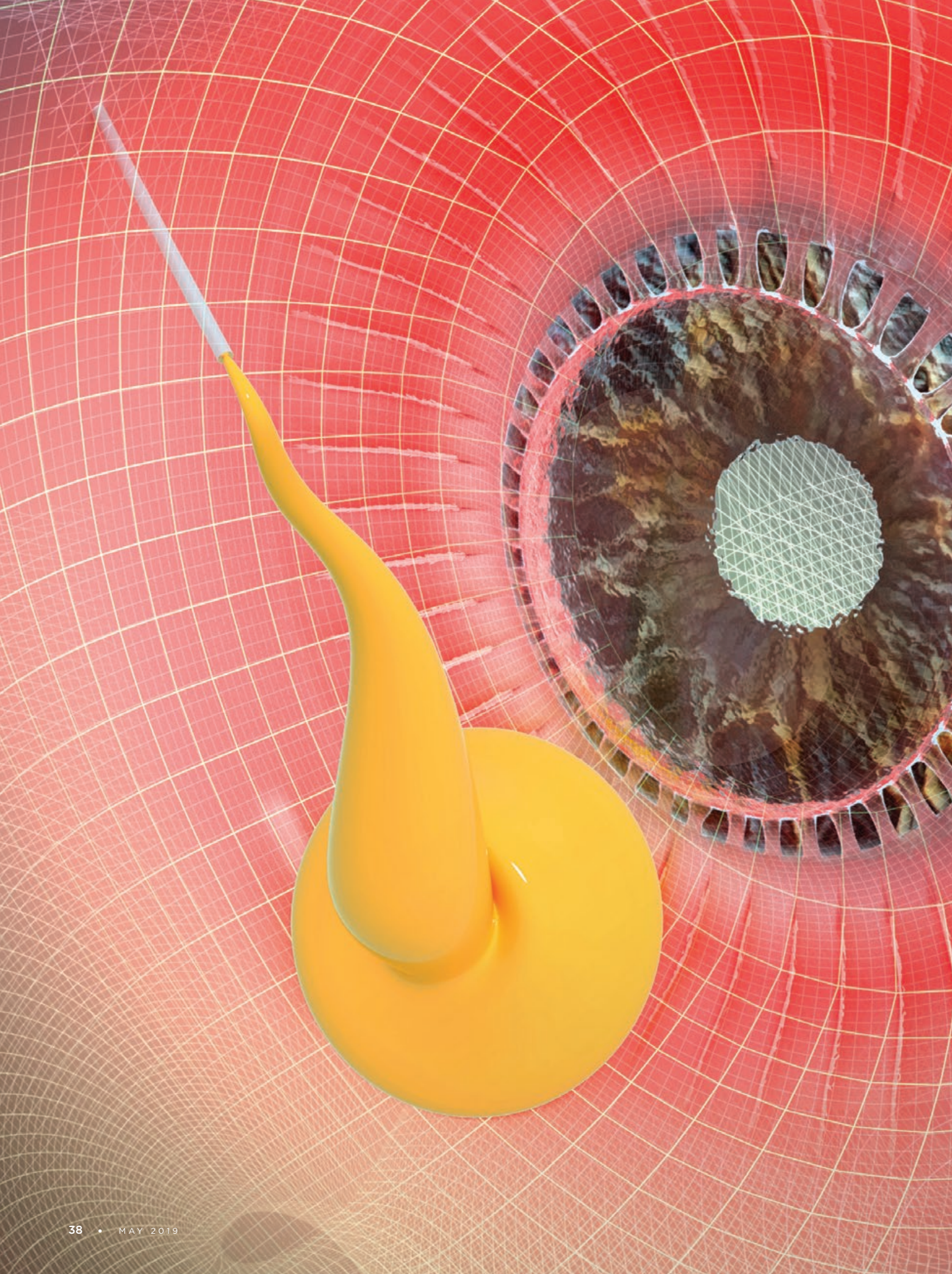
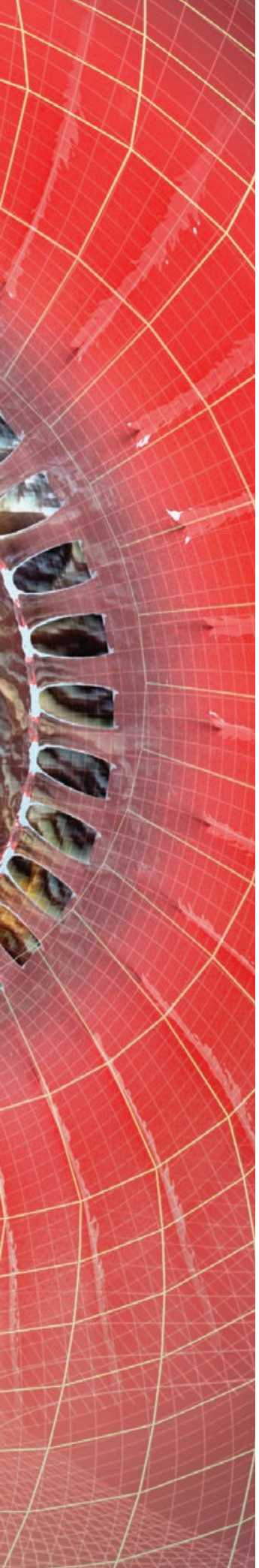
Collin M. McClelland, MD





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Drug Delivery for the Posterior Segment

Born of necessity and scientific advance, new drug delivery devices for treatment of retinal disease and uveitis are now emerging.

By Lori Baker-Schena, MBA, EdD, Contributing Writer

ADVANCES IN POSTERIOR SEGMENT DRUG DELIVERY SYSTEMS ARE occurring at breakneck speed—and are a "welcome and timely addition to our armamentarium," said Dilraj S. Grewal, MD, a vitreoretinal and uveitis specialist.

"The number of patients we are treating has increased exponentially, and often we are seeing them frequently for regular intravitreal injections," said Dr. Grewal, at Duke University in Durham, North Carolina. "We need to find ways to reduce the treatment burden on the patients, of course, as well as on the providers because it takes an entire army to get these injections to the patients every month."

Dr. Grewal sees great promise in the latest developments in drug delivery approaches that are designed to help retina and uveitis patients improve and maintain vision over longer time frames than are provided by currently available treatments. Interestingly, the spate of next-generation devices using sustained-release technology and minimally invasive techniques has its roots in a decades-old history of innovation (see "Legacy of Innovation," page 41).

As the field advances, *EyeNet* asked its editorial board members to indicate which devices—either brand-new to the market or still in trials—they consider the most intriguing or important in terms of potential to change patient care. Then Emmett T. Cunningham, MD, PhD, MPH, founder of the Ophthalmic Innovation Summit, helped refine the list.

For each device, an ophthalmologist close to the product (see financial disclosures, page 44) provided information and opinions. Invariably those who consult or serve as an investigator for emerging products are also the most qualified to knowledgeably discuss them. For more about the ins and outs of reporting on early-stage drugs, devices, and techniques, see Opinion, page 11.

Yutiq

Manufacturer: EyePoint Pharmaceuticals
Status: FDA approved on Oct. 12, 2018; commercially launched on Feb. 4, 2019
Interviewing Quan Dong Nguyen, MD, MSc

How does this technology work?
Approved for the treatment of chronic noninfectious posterior segment uveitis, Yutiq is a nonbioerodible intravitreal microinsert containing 0.18 mg fluocinolone acetonide. It uses the company's proprietary Durasert technology to release the drug consistently over 36 months.

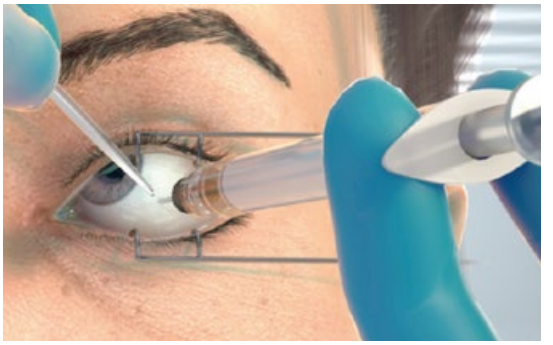
Yutiq is supplied in a sterile single-dose preloaded applicator that can be administered through a 25-gauge needle in the physician's office.

What are the benefits of this device?
Yutiq offers convenience because it can be injected with a small-gauge needle as an office procedure. Also, Yutiq is injected into the vitreous, not anchored in a particular location, so it may reduce the incidence of cataract compared with static placement.

According to the company, you can use J-code J7313 to bill for 18 units.

What are the research findings?
In a phase 3, double-masked, randomized trial, 87 eyes of patients with chronic noninfectious posterior segment uveitis were treated with Yutiq and 42 eyes received sham injections.[1] At 24 months of the three-year trial, the recurrence rate in Yutiq eyes was 59.8% versus 97.6% with the control eyes. Macular edema was resolved in 84.1% of Yutiq-treated eyes and 57.1% of control eyes that had edema recorded at baseline. Drops to lower intraocular pressure (IOP) were used in 41.4% of Yutiq treated eyes and 33.3% of control eyes. Cataracts were extracted from 64.3% of Yutiq patients with phakic eyes and 14.3% of control patients with phakic eyes.

What are the drawbacks to this device?
Before inserting this device into the vitreous of potential patients, physicians must thoroughly evaluate the uveitis to rule out any infectious causes. Yutiq is indicated for noninfectious uveitis, and if a case is of infectious etiology, the steroid insert could activate the pathogen. Additionally, physicians need to discuss with the patients the potential risk of cataract worsening and IOP elevation.



How has the device affected patient quality of life?
In selected patients—whether the disease manifests solely in the eye or in association with systemic diseases—it is not advised to employ systemic treatment, with its potentially debilitating side effects, when local therapy may be possible to control the inflammation and preserve the vision. Yutiq has shown that it can help patients achieve and maintain inflammation control, thus potentially decreasing disease recurrences and preventing cumulative ocular damage that can lead to suboptimal visual function.

Xipere

Manufacturer: Clearside Biomedical
Status: Phase 3 trials complete; NDA submitted to FDA on Dec. 19, 2018
Interviewing Rahul N. Khurana, MD

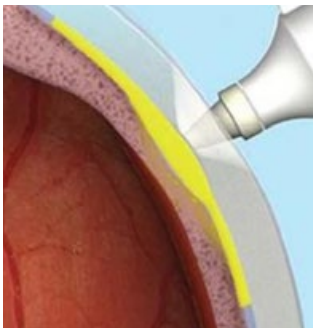
How does this technology work?
Xipere (formerly suprachoroidal CLS-TA) is a proprietary suspension of triamcinolone acetonide for treatment of macular edema associated with uveitis. It is formulated for injection in the suprachoroidal space using a microneedle measuring 1,000 µm in length. Once injected, the corticosteroid rapidly disperses to the choroid and retina, where it is designed to remain for an extended amount of time. The injection can be performed in the clinic.

What are the benefits of this device?
Not surprisingly, ophthalmologists traditionally have tended to associate "suprachoroidal space" with "hemorrhage," assuming that delivering therapeutics to that area would result in complications with bleeding, and that the high choroidal blood flow would wash away the drug. Yet I was excited about the possibility that we could deliver drugs to the choroid and retina while minimizing exposure to the anterior segment—this could be a great

benefit to patients in minimizing complications from steroids. And the research has demonstrated that the incidence of elevated IOP is low compared with other local injections of steroids.

What are the research findings?

The phase 3 PEACHTREE trial randomized 96 patients to receive two 4.0 doses of suprachoroidal CLS-TA 12 weeks apart, and 64 patients as controls to receive a sham procedure at the same 12-week interval.[2] Results showed that 47% of the CLS-TA treated patients gained at least 15 letters in best-corrected visual acuity from baseline at week 24, compared with 16% of control patients. Additionally, the treated patients experienced a mean reduction from baseline of 157 µm at week 24 compared with a 19-µm mean reduction in the control patients. PEACHTREE showed resolution of uveitic inflammation, with 68% of study patients having resolution of vitreous haze versus 23% in the control arm.



No serious adverse events were reported. Elevated IOP included high pressure, ocular hypertension, and glaucoma. All told, 9.4% had elevated IOP of greater than 10 mm Hg; 10% were prescribed IOP-lowering drops.

What are the drawbacks to this device?

With any new technology, there will be a learning curve for mastering the technique; it will take time for retina specialists to get comfortable accessing the suprachoroidal space. But we are accustomed to doing injections in the vitreous already, and it's a relatively small step to learn to inject into the suprachoroidal space.

In addition, 12% of study patients complained of eye pain during the procedure compared with 4.7% of controls, and the pain resolved after the procedure.

A Legacy of Innovation

Today's innovations are part of a pioneering legacy in research for vitreoretinal diseases. Dr. Grewal points to Vitrasert (Chiron, later Bausch + Lomb), the first sustained-release posterior segment drug delivery system that laid some of the foundation for today's breakthroughs. Approved by the FDA in March 1996, Vitrasert consists of a 4.5 mg pellet of ganciclovir coated with a biocompatible polymer and is designed to deliver the drug over five to eight months. It was indicated for the local treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome (AIDS).

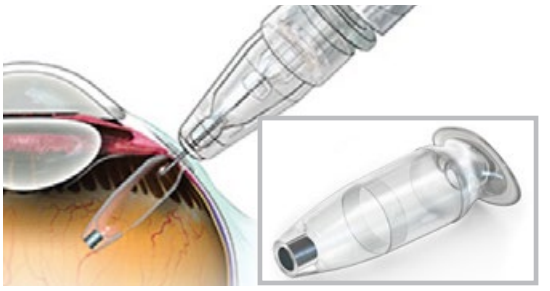
Other breakthroughs that followed included:

- **Retisert (Bausch + Lomb).** The FDA approved this intravitreal implant on April 8, 2005, for the treatment of chronic noninfectious uveitis affecting the posterior segment. Its microdrug reservoir contains 0.59 mg fluocinolone acetonide and delivers sustained levels of the drug for approximately 30 months. "This is a great product in terms of controlling inflammation but requires surgery for placement, and its side effects are increased incidence of cataract and IOP elevation, which may also require concurrent or additional surgery for control," Dr. Grewal said.
- **Ozurdex (Allergan).** This biodegradable sustained-release intravitreal corticosteroid implant containing 0.7 mg dexamethasone, designed to last approximately six months, was FDA approved for the treatment of macular edema following retinal vein occlusion on June 17, 2009, said Dr. Grewal. It was approved for treatment of noninfectious uveitis affecting the posterior segment of the eye in 2010 and diabetic macular edema in 2014.*
- **Iluvien (Alimera).** The FDA approved this nonbioerodible, sustained-release intravitreal implant on Sept. 26, 2014, for the treatment of diabetic macular edema. It delivers 36 months of continuous low-dose corticosteroid dosing with a single injection.

"We continue to see good safety data on the long-term tolerance of these sustained-release drug delivery systems as well as their effectiveness," said Dr. Grewal.

*On Dec. 28, 2018, Allergan voluntarily recalled 22 lots of Ozurdex, noting that a silicone particle of approximately 300 µm in diameter may detach from the needle sleeve during administration.

How has the device affected patient quality of life?
Xipere represents an approach that is viable and extremely efficacious. Data from the phase 3 trial show that 1 in 2 patients had significant vision gain with resolution of macular edema, and 2 of 3 patients had resolution of their intraocular inflammation.



Port Delivery System

Manufacturer: Roche/Genentech
Status: Phase 3 trial began in September 2018
Interviewing Carl C. Awh, MD

How does this technology work?
The Port Delivery System with ranibizumab (PDS) consists of a permanent intraocular implant filled with a specialized formulation of ranibizumab. The device, which is slightly longer than a grain of rice, is surgically implanted at the pars plana and covered by conjunctiva and Tenon capsule. It can be refilled in the office using a customized needle. The PDS provides continuous delivery of ranibizumab into the vitreous.

What are the benefits of this device?
The PDS may reduce the treatment burden on patients, caregivers, and physicians. Real-world analyses consistently demonstrate that [because of treatment burden] many patients with neovascular AMD (nAMD) receive fewer than the optimal number of intravitreal injections over time, with outcomes inferior to those demonstrated in pivotal trials.[3]

Continuous delivery of ranibizumab into the vitreous with the PDS offers an expected interval between in-office refills that is significantly longer than the current monthly or bimonthly intravitreal anti-VEGF injections, and it has the potential for equivalent outcomes.

What are the research findings?
The phase 2 LADDER (Long Acting DElivery of Ranibizumab) trial compared the PDS to monthly ranibizumab injections in patients with nAMD and a history of favorable response to prior anti-VEGF treatment.[4] The trial enrolled 243 patients and evaluated three different doses of ranibizumab in the PDS. Outcomes were favorable in all groups, but of particular note were the outcomes in the highest dose group using 100 mg/mL. Most patients in this group (80%) went at least six months without requiring a refill, with a median time to first refill of 15 months. In addition, vision outcomes were comparable to those achieved with monthly ranibizumab injections.

What are the drawbacks to this device?
A surgical procedure in the OR is necessary to implant the PDS and this must be considered when comparing the PDS to standard intravitreal injections. In the LADDER trial, the optimized surgical and refill procedures were generally well tolerated. In the PDS arms, the rate of postoperative vitreous hemorrhage with the optimized surgery procedure was 4.3%. The rate of endophthalmitis in the primary analysis population was 1.6%. We will learn more in the phase 3 trial. As with all surgical procedures, there will be continual refinement as surgeons gain experience.

How has the device affected patient quality of life?
In the LADDER trial, patients with the PDS were evaluated monthly, so there was no reduction in office visits. However, if the phase 3 trial shows similar outcomes and leads to commercial availability, there could be significant improvements in outcomes for patients who might otherwise struggle to get the optimal number of intravitreal injections.

GB-102 for Wet AMD

Manufacturer: Graybug Vision
Status: Phase 1/2a study initial data analysis reported January 2019; phase 2b study enrollment expected to begin in 2019
Interviewing Pravin U. Dugel, MD

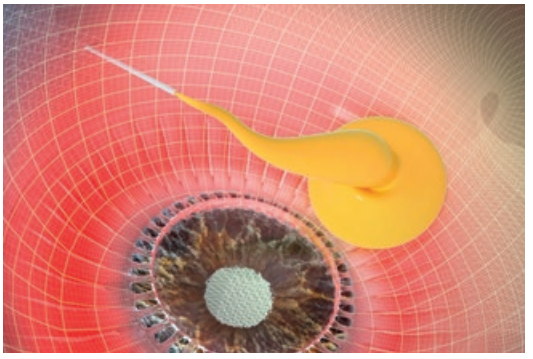
How does this technology work?
GB-102, for the treatment of wet AMD, encapsulates sunitinib malate within bioabsorbable microparticles. After intravitreal injection (IVT), these particles aggregate to form a depot in the inferior vitreous. This depot elutes the drug such that IVT may be necessary only twice a year. Sunitinib blocks cell receptors associated with angiogenesis, proliferation, vascular permeability, and fibrosis.

What are the benefits of this device?
GB-102 will allow us to provide a more sustainable treatment strategy. In contrast to monthly injections, GB-102 delivers the drug on a constant rather than pulsatile basis. Also, because it is a tyrosine kinase inhibitor delivery device, it has possibilities for wider applications, such as treatment of diabetic macular edema and retinal vein occlusion.

What are the research findings?
In the phase 1/2 ADAGIO study, GB-102 demonstrated safety and efficacy, with the duration of effect reaching six to eight months from a single IVT injection.[5] The study involved 32 patients with wet AMD who were evenly divided into four dosing groups: 0.25 mg, 0.5 mg, 1 mg, and 2 mg. GB-102 was well-tolerated with no dose-limiting toxicities, drug-related serious adverse events, or inflammation, and 88% and 68% of patients were maintained on a single dose of GB-102 at three and six months, respectively.

What are the drawbacks to this device?
In the clinical trial, at the highest dose, some microparticle dispersion caused a slight decrease in visual acuity. A new manufacturing process was developed that eliminated the microparticle dispersion, and this newer version of the drug will be used for phase 2b clinical studies.

How has the device affected patient quality of life?
Current treatment alternatives for wet AMD illustrate the great divide between clinical studies and real life. Whereas clinical studies are done in a pristine fashion, the reality is that patients have a difficult time handling the monthly IVT injection requirements. Taking off work, finding a ride, depending on a caregiver—this is a huge treatment burden on the patient and is not reflected in clinical trials. I see this new technology closing the gap and reducing the number of injections necessary to positively impact the patient's quality of life.



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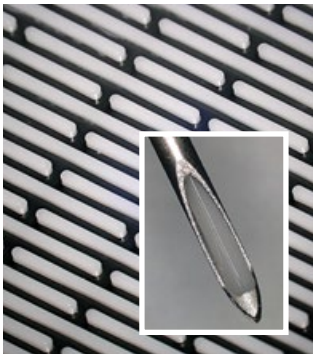
Dexamethasone Intravitreal Implant (AR-1105) With PRINT Technology

Manufacturer: Aerie Pharmaceuticals
Status: AR-1105 phase 2 trial began in spring 2019; AR-13503 (Rho kinase/protein kinase C inhibitor) phase 2 trial to be initiated Q2 2019
Interviewing Theresa G.H. Heah, MD, MBA

How does this technology work?
AR-1105 is a bioerodible implant for treatment of patients with macular edema due to retinal vein occlusion or diabetic macular edema. Delivered through an intravitreal injection using a 25-gauge needle, the implant is intended to release dexamethasone over a six-month period. It uses PRINT (particle replication in nonwetting templates) technology in which a mold is created that contains precisely shaped and sized drug particles from the nanometer to millimeter range. This technology allows for drug delivery directly to the back of the eye and control of the elution rate.



What are the benefits of this device?
The potential benefits include six-month duration of sustained efficacy, improved administration due to a smaller needle size, and possibly a better safety profile due to lower peak drug levels.

The versatility of the PRINT technology also allows us to explore novel drug pathways in retinal disease. For example, in the first quarter of 2019 the company filed an investigational new drug (IND) application with the FDA for its second retinal product—a bioerodible implant containing the Rho kinase/protein kinase C inhibitor AR-13503 to treat wet AMD and diabetic macular edema via a 27-gauge needle with an intended release over a four- to six-month period.

What are the research findings?
A study was conducted focusing on the reproducibility and uniformity of PRINT manufacturing using dexamethasone intravitreal implants.[6]

Results showed that PRINT could be used to manufacture fully biodegradable dexamethasone intraocular implants with uniform size, shape, and dosages—with high reproducibility.

What are the drawbacks to this device?
One challenge: ensuring the drug molecules can be kept in an efficacious concentration in the implant.

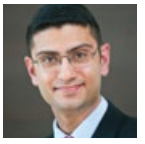
How has the device affected patient quality of life?
We believe that AR-1105 and AR-13503 will potentially provide a longer duration of efficacy with reduced number of injections, positively impacting patients' quality of life.

1 Nguyen QD. 24-month evaluation of fluocinolone acetonide intravitreal insert treatment for noninfectious posterior uveitis. Presented at Retina Subspecialty Day 2018, Oct. 26, 2018; Chicago.
2 Khurana RN. Suprachoroidal delivery of CLS-TA for uveitic macular edema: Results of the phase 3 PEACHTREE trial. Presented at Uveitis Subspecialty Day 2018, Oct. 27, 2018; Chicago.
3 Ciulla TA et al. *Ophthalmol Retin.* 2018;2(12):1179-1187.
4 Awh C. LADDER trial of the port delivery system for ranibizumab: Preliminary study results. Presented at the Annual Meeting of the American Society of Retina Specialists, July 25, 2018; Vancouver, British Columbia, Canada.
5 Boyer DS. New developments in drug therapy for retinal disorders. Presented at the Hawaiian Eye & Retina Annual Meeting, Jan. 21, 2019; Kona, Hawaii.
6 Sandahl M et al. *Invest Ophthalmol Vis Sci.* 2018;59(9):5671.

Meet the Experts

Carl C. Awh, MD Vitreoretinal surgeon and president of Tennessee Retina in Nashville, Tenn. *Financial disclosures: Allergan: C; Apellis Pharmaceuticals: S; ArcticDx: C,O,P; Bausch + Lomb: S,C; Genentech: S,C; Hoffman-LaRoche: S; Katalyst Surgical: C,O,P; Merck: S; Ophthotech: S; PanOptica: S; Volk: C.*

Pravin U. Dugel, MD Vitreoretinal surgeon and managing partner of Retinal Consultants of Arizona in Phoenix. He is a clinical professor of the Roski Eye Institute at the Keck School of Medicine at the University of Southern California. *Financial disclosures: Acucela: C; Aerie: C; Aerpio: C,O; Alcon: C; Alimera: C,O; Allergan: C; Amgen: C; AMO: C; Annidis: C,O; ArcticDx: C,O; Avalanche: C; Bausch + Lomb: C; Beyeonics: C; Boehringer Ingelheim: C; CDRLife: C; Chengdu Kanghong: C; Clearside: C,O; Digisight: C,O; Dose Medical: C; Genentech: C; Graybug Vision: C; Irenix: C,O; Kodiak Sciences: C; Lutronic: C; Lux BioScience: C; Macusight: C; NeoVista: C; Neurotech: C; Novartis: C; Oculis SA: C; Omeros: C; Ophthotech: C,O; Opthea: C; Optovue: C; ORA: C; Orbis: C; PanOptica: C,O; Pentavision: C; pSivida: C; QLT C; Regeneron: C; Roche Diagnostics: C; Santen: C; SciFluor Life Sciences: C; Shire Human Genetics: C; Spark: C; Stealth Biotherapeutics: C; ThromboGenics: C; Topcon: C; TrueVision: C; Zeiss: C.*



Dilraj S. Grewal, MD Vitreoretinal and uveitis specialist, and associate professor of ophthalmology at the Duke University School of Medicine in Durham, N.C. *Financial disclosures: Alimera: C; Allergan: C; Clearside: C.*

Theresa G.H. Heah, MD, MBA Ophthalmologist and vice president of Clinical Research, Medical and Professional Affairs, Aerie Pharmaceuticals in Bedminster, N.J. *Financial disclosures: Aerie: E,O.*

Rahul N. Khurana, MD Vitreoretinal surgeon and partner at Northern California Retina Vitreous Associates in Mountain View, Calif., and a clinical associate professor of ophthalmology at the University of California, San Francisco Medical Center. *Financial disclosures: Alkahest: C; Allergan: C,S; Clearside Biomedical: C,S; Genentech: C; Regeneron: C; Roche: S; Santen: S.*

Quan Dong Nguyen, MD, M.Sc. Uveitis specialist and vitreoretinal surgeon and professor of ophthalmology at the Byers Eye Institute at the Stanford University School of Medicine in Palo Alto, Calif. *Financial disclosures: AbbVie: C; Bayer Healthcare: C; EyePoint: C; Genentech: C; Gilead: C; Regeneron: C; Santen: C.*

See disclosure key, page 8.

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Subspecialty Day October 11 – 12
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Discover Invaluable Pearls in the Jackson Memorial Lecture

Emily Y. Chew, MD, will deliver the most prestigious lecture in ophthalmology — the 76th Edward Jackson Memorial Lecture, titled "Age-related Macular Degeneration: Nutrition, Genes and Deep Learning." Dr. Chew's talk will offer pearls on diabetic- and age-related eye diseases.

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AAO 2019

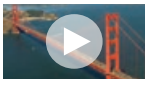
Explore What's New at AAO 2019

Enhanced Scientific ePoster Theatre and Lounge – Examine e-posters on large touch-screens and interact with presenting authors.

American Society of Ophthalmic Registered Nurses The two-day ASORN nursing track is now officially part AAO 2019.

Stimulate Your Senses in San Francisco

The Bay Area boasts 57 Michelin-starred restaurants. Don't miss the chance to dine at Atelier Crenn, headed by chef Dominique Crenn, the first female chef in the United States to earn three stars.



Watch this short video at **aao.org/2019** and discover what inspires you.

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Best Practices for Coding, Part 2: Reduce Denials and Keep Payments on Track

To help you stay current on payers' ever-changing coding rules, *EyeNet* published "Best Practices for Coding: Six Do's and Don'ts" in the January 2019 Savvy Coder (available at aao.org/eyenet/archive). This follow-up article provides six more tried-and-true strategies.

Best Practices 7 Through 12

7. Have a consistent process for alerting staff and physicians about coding updates. The requirements for coding and documentation are constantly in flux, and your compliance plan should include procedures for communicating such changes throughout the practice, whether by email, via interoffice memo, or in a staff meeting.

8. Catalog your communications on coding updates. By keeping a record of changes to your coding policies, you create a historical resource that could be critical in an audit. Remember that documentation must support the policy that was in place at the time of the encounter. Furthermore, if an audit outcome isn't positive, the payer will take into consideration any evidence that demonstrates your desire to be compliant.

9. Verify insurance every time. For each office visit, confirm the details of the patient's insurance—ideally before the patient presents at the practice. Do this even for established patients, since they may change or lose insurance at any point during the calendar year.

10. Get preauthorization for surgeries and some tests. Preauthorization—also known as prior authorization, precertification, or prenotification—involves contacting the payer and obtaining a certification number for you to include when you submit your claim for a service. Medicare Advantage plans, Medicaid plans, and commercial plans change their preauthorization requirements often. (Medicare Part B doesn't require preauthorizations.)

Note: Preauthorization for a surgery doesn't necessarily take into consideration coverage of every test; nor does it consider Correct Coding Initiative (CCI) bundling edits, which is why you should always check with the payer to see whether multiple CPT codes can be paid when the services that they represent are performed during the same session. (Many payers have a look-up feature on their website.) To help you with preauthorization, the Academy has published a detailed checklist (see a link for it at aao.org/practice-management/coding/updates-resources).

11. Correct and resubmit denied claims within 24 hours. When submitted electronically, a clean claim—meaning one without errors—typically takes 14 days to process. If a claim is denied, promptly submit a corrected form to keep payments on track.

Common reasons for denial include:

- patient's name is not listed as it appears on his or her insurance card;
- site of service issues;
- wrong or missing modifier;
- CCI edits not followed;
- mislinked diagnosis; and
- frequency edits on Eye visit codes or testing services.

Tip: Keep a list of denials and share it with all in your practice so that the same denials are not perpetuated.

12. Know which commercial payers still recognize consultation codes. A few commercial payers still recognize the 99241-99245 code family, but CMS and Medicare discontinued payment for these consultation codes a long time ago (Jan. 1, 2010). Consequently, if you include Medicare as the secondary payer for a consultation code (whether it is for an office or an inpatient exam), you will end up writing off the 20% balance.

Help Us to Help You

Boost Academy advocacy: Tell us about your preauthorization problems. The Academy's D.C. office is working to reduce—and perhaps eliminate—the administrative burden of preauthorization. If you've had cases in which preauthorization delayed medical care and/or instances where payment was denied even with preauthorization, please email coding@aao.org.

EXTRA **MORE ONLINE.** For nine key (and free) resources, see this article at aao.org/eyenet.

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

Academy Notebook

NEWS • TIPS • RESOURCES

ADVOCATE. *Academy members volunteered to advocate to senators on ophthalmic issues during Congressional Advocacy Day 2018.*

WHAT'S HAPPENING

Academy Creates Volunteering Web Page

Many Academy members volunteer their time and talent on Academy committees. Many more members would like to volunteer, but committee opportunities are limited.

In March, the Academy launched a concise volunteering web page in the Member Services area of aao.org. This guide is designed to increase awareness among members of the many volunteer opportunities available outside the scope of committee work. It describes opportunities to speak, write, review, advocate, connect, and develop interactive content to further the work of various Academy programs. Each opportunity provides instructions and outlines expectations.

This effort is intended to help members find volunteer opportunities, enhance member engagement, and strengthen Academy programs.

To get involved, visit aao.org/member-services/volunteer.

Support the Museum's Permanent Location

Until now, the Academy's 38,000-piece Museum of Vision collection has been accessible only by appointment or online. With your support, the Academy will build a permanent home on the ground floor of its headquarters with five galleries and state-of-the-art interactive displays. The museum will open to Academy members during AAO 2019, with a grand opening to the public in 2020. The Academy anticipates welcoming more than 30,000 visitors in the first year alone.

Explore the collection at aao.org/museum and contribute toward the Academy's $12 million goal to build the Museum of Vision at aao.org/museum-campaign.

TAKE NOTICE

2019 MIPS: June 1 Deadline for EHR-Based Reporting

The IRIS Registry can streamline your reporting for the Merit-Based Incentive Payment System (MIPS) as long as you meet the appropriate deadlines.

Report quality measures using automated data extraction. The least burdensome way to report MIPS quality measures is to integrate your electronic health record (EHR) system with the IRIS Registry.

June 1 deadline for getting started with IRIS Registry/EHR integration. If you haven't yet integrated your EHR system with the IRIS Registry, you must sign up or—if you signed up last year but didn't integrate—notify the IRIS Registry by June 1 and complete the integration process by Aug. 1.

The IRIS Registry is a one-stop shop for MIPS reporting. You also can use the IRIS Registry to manually attest to promoting interoperability (PI) measures and improvement activities, and—if you aren't able to report quality via IRIS Registry/EHR integration—manually enter data for quality measures. If you are new to the IRIS Registry, you will need to sign up for manual reporting by Oct. 31.

For more information, go to aao.org/iris-registry/medicare-reporting.

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In Private Practice? Apply for Research Grant by May 31

A research fund established last year gives Academy members in private practice an opportunity to harness the power of big data—but those interested must submit their applications by May 31. The H. Dunbar Hoskins Jr., MD, Center for Quality Eye Care IRIS Registry Research Fund will support at least four IRIS Registry analytics projects in 2019.

Learn more about the eligibility requirements and the application process at aao.org/iris-registry/data-analysis/hoskins-center-research-fund.

Follow @AAOjournal for the Latest Research

Stay up-to-date on research from *Ophthalmology, Ophthalmology Retina,* and *Ophthalmology Glaucoma* on Twitter. Content is posted every day including articles in press, "Pictures & Perspectives," editorials, and new issue alerts.

Follow @AAOjournal at twitter.com/AAOjournal.

Submit Your Research to *Ophthalmology Glaucoma*

Last summer, the Academy and the American Glaucoma Society collaborated in launching *Ophthalmology Glaucoma.*

This journal provides an opportunity to disseminate your glaucoma research directly to those who find it most relevant. Joining the ranks of the Academy's esteemed *Ophthalmology* and *Ophthalmology Retina, Ophthalmology Glaucoma* provides readers with innovative, peer-reviewed works on a bimonthly basis.

Submit your original research at www.evise.com/profile/#/OGLA/login.

Subscribe at www.ophthalmologyglaucoma.org.

D.C. REPORT

Loss of '15 Letters of Visual Acuity': One Medicare Advantage Plan's Definitions of Step Therapy Failure

The Centers for Medicare & Medicaid Services now permits Medicare Advantage plans to use fail-first policies for Part B drugs. A Medicare Advantage plan that currently serves Idaho, Montana, and Oregon defines an anti-VEGF drug's failure as resulting in patients' worsening vision after a minimum three-month trial, "such as losing greater than 15 letters of visual acuity."

At least eight other Medicare Advantage plans are implementing step therapy in 2019 to curtail physicians' choice in treating patients. Many requirements for intravitreal anti-VEGF therapy are similarly egregious. Some require three months of failed treatment before the physician can administer a different drug.

The Academy, along with Prevent Blindness and American Society of Retina Specialists, is focused on convincing the executive branch that step therapy interferes with the patient-physician relationship. If you have had negative experiences with step therapy, you can support the Academy's efforts by relaying the following to www.preventblindness.org/patient-step-therapy-stories:

- the condition you treated;
- the medication that was first recommended and then denied;
- the reason for the denial; and
- the case's outcome.

ACADEMY RESOURCES

Order the Updated 2019-2020 *BCSC*

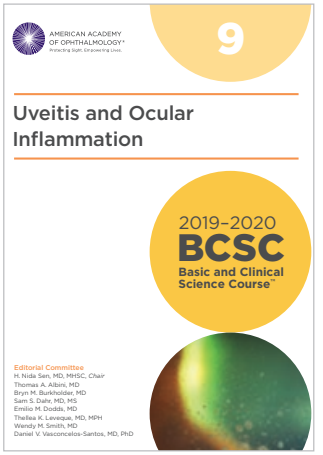
The 2019-2020 edition of the *Basic and Clinical Science Course (BCSC)*, the definitive source of clinical information for ophthalmologists and residents throughout the world, is available for advance order starting in mid-May and will ship by mid-June (eBooks are available starting in mid-June).

The 2019-2020 edition includes major revisions to the following:

- Section 1: Update on General Medicine;
- Section 2: Fundamentals and Principles of Ophthalmology;
- Section 7: Oculofacial Plastic and Orbital Surgery; and
- Section 9: Uveitis and Ocular Inflammation.

Choose from the print or eBook format. Purchase an individual section or save when buying a complete set of all 13 sections of the *BCSC.*

Find pricing and information at aao.org/bcsc.



Get Updated Fundamental Surgical Texts

Residents and trainees, build a solid foundation of ophthalmic surgical knowledge with new editions of *Basic Principles of Ophthalmic Surgery,* fourth edition, and *Basic Techniques of Ophthalmic Surgery,* third edition. Together, these books provide step-by-step instructions for more than 80 common procedures. Images and videos are used extensively to increase understanding.

These essential texts are available for advance order starting in mid-May and will ship by mid-June (eBooks are available starting in mid-June). Both texts are available in print or eBook format and are included in 2019-2020 *BCSC Residency Sets.*

Find pricing and information at aao.org/bcsc.

Destination AAO 2019

GET READY FOR SAN FRANCISCO • PART 1 OF 6

WELCOME

Get Inspired in San Francisco

It's time to start preparing for the world's largest, most comprehensive ophthalmic meeting. At AAO 2019, you'll have the opportunity to learn from leaders in the field, discuss hot topics in medicine, connect with colleagues, and explore the city.

When to be there. AAO 2019 runs Oct. 12-15 and is preceded by Subspecialty Day programs, held Oct. 11-12. You can also attend AAOE's program Oct. 11-15.

How to prepare. Over the next five months, this "Destination AAO 2019" section will guide you through deadlines, preview the scientific program, and highlight key events.

SPOTLIGHT ON SKILLS TRANSFER LABS

Dr. Cohen's Insider Perspective

Jack A. Cohen, MD, FACS, is currently serving his fifth year as Chair of the Skills Transfer Program, his eighth on this committee. Below, Dr. Cohen previews the Skills Transfer learning opportunities at AAO 2019.

Q: What are the Skills Transfer labs?

A: The Skills Transfer labs are provided by the Academy at the annual meeting for physicians to learn or relearn skills that they want to perform. Ophthalmology and other medical specialties are changing so quickly: New studies are constantly coming out, as are new techniques, drugs, and equipment.

Jack A. Cohen, MD, FACS.

Q: What is the structure of the labs?

A: During the labs, we provide pig eyes, human eyes—all sorts of models, as well as equipment that allows participants to simulate performing eye surgery on a real person. We try to make the ratio of attendees to instructors as close to one-to-one as possible.

Thirty-five of the 57 courses have related didactics, meaning that a separate lecture takes place a couple of hours before the lab, a day before, etc. This allows participants to gain some knowledge before they sit down and start doing a technique that they haven't otherwise studied.

Q: How are the labs planned?

A: It starts with the Skills Transfer Program Committee, which comprises members from various subspecialties. The group meets twice a year, once shortly after the annual meeting and once in January. At both committee meetings, we review the labs and determine which were successful and unsuccessful, and which could be improved. At the January meeting in particular, we look at what's hot in ophthalmology and consider new courses. For instance, what's hot right now is placement of IOLs without sufficient support, or gluing and suturing of lenses.

Q: How are the labs executed?

A: It's like an orchestra with different parts that all come together on the day of the course. These labs require models, animal and human eyes, microscopes, and special machines. Central to the labs' execution is Susan Oslar, the Academy's Technical Programs Manager. We also rely on the help of instructors, all of whom are volunteers and often very busy.

Q: What's new for AAO 2019?

A: We are focused on making things clearer for the participants—we always want them to know what they are signing up for. For example, we have revised some course descriptions to make them more accurate. Several courses offer multiple techniques, and often participants will walk in and say, "I want to do all these techniques," which doesn't always work with our time frame. This year, these labs will have a poster that lists the techniques, explains how they differ, and tells participants how many techniques they may choose to learn. We hope this eliminates any confusion about expectations.

Q: What is one of the best memories

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or experiences you've had with this program?

A: Last year, I took a course on IOL placement because I wanted to experience a Skills Transfer lab firsthand. As a retina specialist, I was excited to take the lab because I do a lot of suture fixation and thought the course might expand my repertoire. What I experienced was phenomenal. I had one-on-one instruction, and my instructor was fantastic: He was patient, courteous, and kind; he showed me videos; and he took extra time to explain things to me. It was nice to see what the courses are like from a participant's perspective.

Q: Who should take a Skills Transfer lab?

A: We offer courses for all physicians; it's just a matter of need. Our 57 courses cover cataract, cornea, plastics, retina, glaucoma, and skills with testing/imaging interpretation.

The skills we offer also vary from simple to complex. Many of the simpler ones are excellent for residents who want to enhance what they're learning in their residency programs.

BEAT THE CLOCK

Registration and Hotels Open Next Month

Get ready to attend AAO 2019 in San Francisco, Oct. 12-15. On June 12, Academy and AAOE members can register and reserve hotel rooms. Nonmembers can do so starting June 26. Online registration will remain open through the meeting.

Fraud alert! Several fraudulent companies, pretending to be associated with the Academy and AAO 2019, may appear in web searches or may have contacted you via email. These companies claim that they can book hotel rooms and/or register you for the Academy's annual meeting, but they are unaffiliated with the Academy. Make sure that you book only through the Academy's website and AAO 2019's official hotel reservation provider, Expovision.

If you are ever in doubt, email meetings@aao.org or call 415-561-8500. You can also contact Expovision directly at aaohotels@expovision.com, or call toll-free at 866-774-0487.

Find more information at aao.org/registration and aao.org/hotels.

Course Pass and Tickets: Buy Them Early

Registration for AAO 2019 gives you access to all Spotlight sessions, symposia, papers sessions, e-posters, videos, Academy Café sessions, and more.

Academy Plus. Purchase an Academy Plus course pass for unlimited access to all Academy and AAOE instruction courses, including Skills Transfer lectures.

Ticketed Events. The following courses are special offerings not covered by general registration or the Academy Plus course pass and must be purchased separately:

- AAOE Practice Management Master Classes;
- Friday AAOE Coding Master Class and Saturday Coding Sessions;
- Skills Transfer labs;
- Subspecialty Day meetings; and
- Specific special meetings and events.

Seats for these sessions are limited. Remember to purchase tickets early. Course pass and ticket prices rise Aug. 8.

Visit aao.org/registration for more information.

PROGRAM

Attend Subspecialty Day

Subspecialty Day meetings feature world-renowned ophthalmologists presenting the latest developments and pearls in the field of ophthalmology. When you register for a meeting, you can float among all the Subspecialty Day meetings taking place that day. Meeting dates are as follows:

One-day meeting on Friday, Oct. 11.

- Refractive Surgery: As Far as the Eye Can See

Two-day meeting on Friday, Oct. 11, and Saturday, Oct. 12.

- Retina: I^2—Inspire Innovation

One-day meetings on Saturday, Oct. 12.

- Cornea: Keeping Disease at Bay
- Glaucoma: Crossing the Golden Gate to Exceptional Glaucoma Care
- Neuro-Ophthalmology: Diagnostic Errors and Challenges—Avoid the Traps!
- Oculofacial Plastic Surgery 2010-2019: A Decade to Remember
- Pediatric Ophthalmology: San Francisco Sound Meets Science

Register. Online registration for Subspecialty Day meetings opens June 12 for Academy and AAOE members. Nonmembers may register starting June 26. Visit aao.org/subspecialty-day for more information.

Improve Your Practice With the AAOE Program

Discover innovative ways to increase practice efficiency: Attend the AAOE Program, Oct. 11-15. Choose from more than 80 special sessions, which are free with registration, as well as instruction courses on topics ranging from coding to electronic health records. Admission to courses is via the Academy Plus course pass, which must be purchased separately.

For deeper immersion, attend three-hour Master Classes and intensive coding sessions (ticketed separately) on Friday and Saturday.

Review the program at aao.org/aaoe.

Full AAO 2019 Program Information Available in June

Program Search will launch as part of online meeting registration on June 12. Look up annual meeting sessions by day, topic, type of event/course, special interest, or presenter. You don't have to log in or be a member to view program information, though you will need to log in to build a personal calendar and to register.

Learn more about AAO 2019 at aao.org/annual-meeting.

EVENTS

Attend the Red-Carpet Gala

Join the Foundation for lights, cameras, and action at the 2019 Orbital Gala on Sunday, Oct. 13. At this Hollywood, red-carpet–themed fundraiser, you'll have the rare opportunity to dine, bid on silent auction items, and dance the night away at the historic Palace Hotel. All proceeds support the Academy's programs.

Purchase tickets beginning May 16 at aao.org/foundation.

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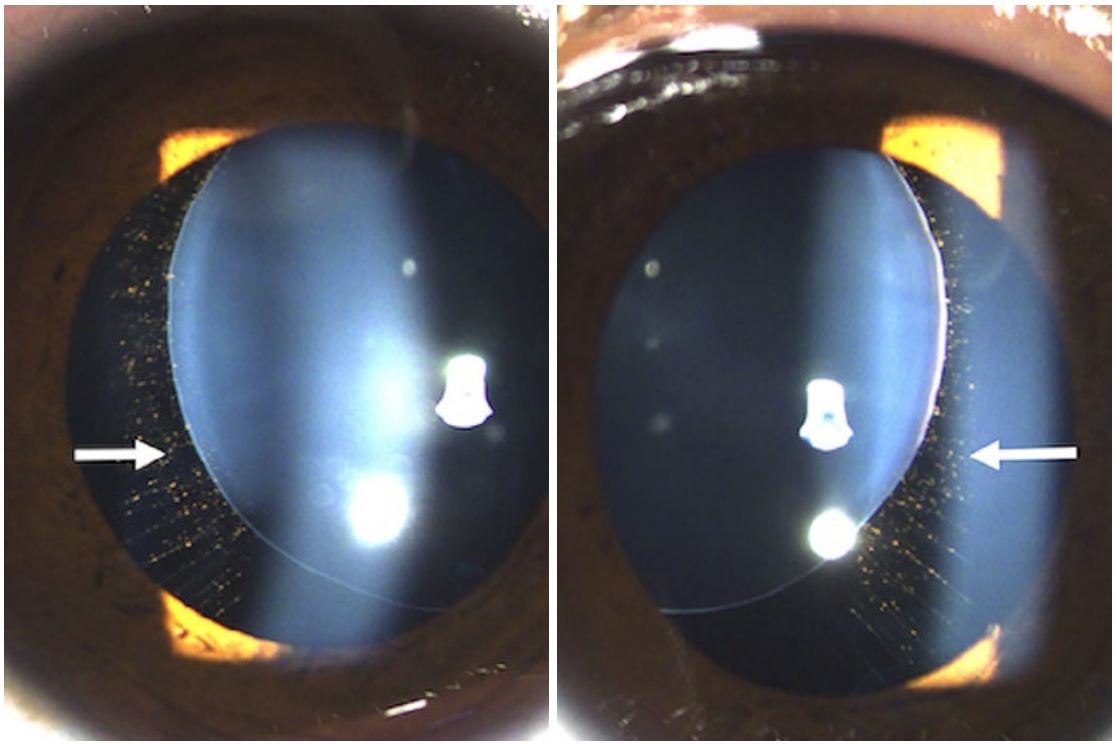
Learn how your support can make a difference at **aao.org/foundation/our-impact**

"When it comes to giving, the decision really comes down to supporting an organization that is most prominent in what we do on a day-to-day basis — and that's the American Academy of Ophthalmology. It's investing in the future of ophthalmology; this is the way we can pay it forward."

WILLIAM F. MIELER, MD, & JENNIFER KANG-MIELER, PHD
LEADERSHIP COUNCIL
WINNETKA, ILL.

MYSTERY IMAGE

BLINK

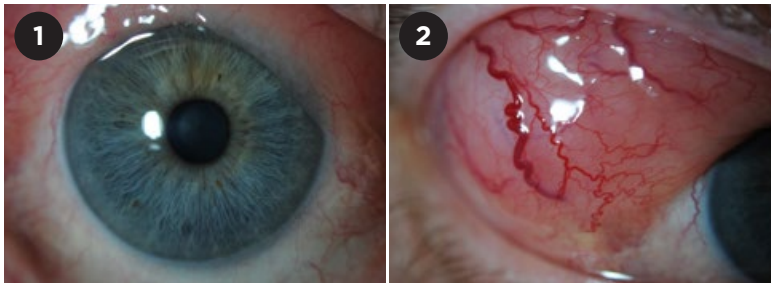


Arun Kapil, Advanced Eye Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

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

LAST MONTH'S BLINK

Conjunctival Lymphoma



A 68-year-old man presented with a two-month history of mild visual blurring and watery discharge from his right eye.

On slit-lamp exam, a large, homogeneous, salmon-colored conjunctival mass (Fig. 1) was noted with enlarged feeder vessels (Fig. 2); these findings raised suspicion of conjunctival lymphoma. He displayed right globe ptosis (5 mm) and proptosis (6 mm)—an external appearance typical of a slowly enlarging mass—without pain or diplopia. Visual acuity was 20/30 in the right eye, and pupillary reactions and color vision were normal.

Computed tomography showed a conforming, homogeneous, soft tissue mass extending from the superior rectus laterally to the lacrimal region and posteriorly behind the orbit to the optic nerve sheath without bony erosion.

Biopsy confirmed the presence of B-cell lymphoma. The patient was referred to a cancer institute for treatment, where a full assessment revealed no involvement beyond the orbit and optic nerve sheath. The suggested treatment was a total dose of 24 Gy external beam radiotherapy, divided in 12 consecutive doses, for stage IAE marginal zone non-Hodgkin lymphoma of the right eye.[1,2]

1 Dhakal B et al. *Clin Lymphoma Myeloma Leuk.* 2017;17(5):305-311.

2 Kirkegaard MM et al. *JAMA Ophthalmol.* 2016;134(4):406-414.

WRITTEN BY **JAIME BADILLA, MD,** AND **SYLVIA H. CHEN, MDCM, MBA, FRCSC,** UNIVERSITY OF ALBERTA, EDMONTON, ALBERTA, CANADA. PHOTOS COURTESY OF ROYAL ALEXANDRA HOSPITAL EYE CLINIC, EDMONTON, ALBERTA, CANADA.

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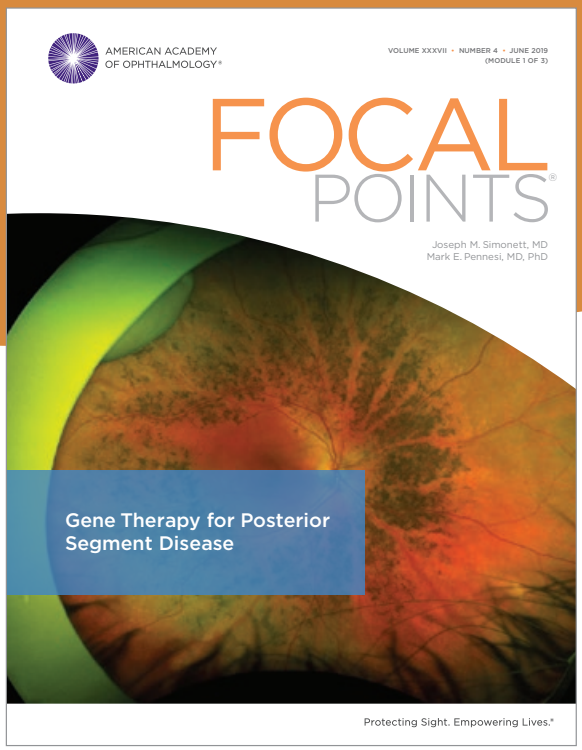

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