WILLS EYE RESIDENT SERIES: A woman presents with decreased vision and burning in her eye, *P. 63*

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JANUARY 2022

Cataract Surgery May Decrease Risk of Developing Dementia

Researchers in the Department of Ophthalmology at the University of Washington-Seattle have found that undergoing cataract surgery decreases the risk of dementia by about 30 percent. The group's results were published online in early December in *JAMA Internal Medicine*.

The prospective, longitudinal study analyzed patients from the Adult Changes in Thought study, a population-based cohort of randomly selected, cognitively normal members of the Kaiser Permanente Washington health-insurance plan. Data on 3,038 patients was collected between 1994 and September 30, 2018. The participants were all at least 65 and dementia-free at enrollment, and were followed until incident dementia. Only patients with a diagnosis of cataract or glaucoma before enrollment or during follow-up were included.

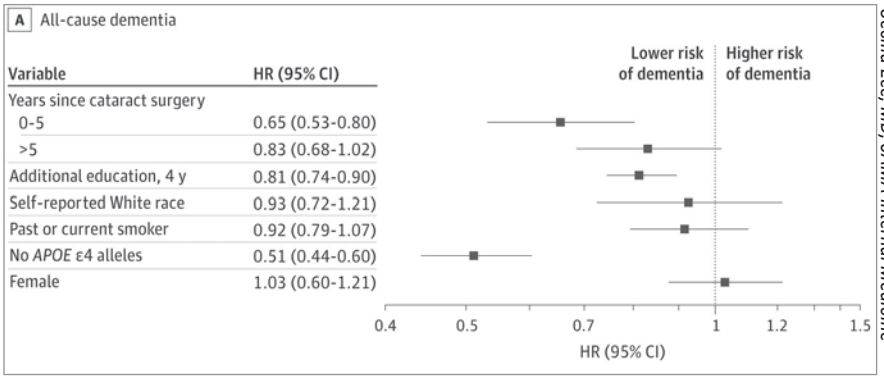
The investigators say that, based on 23,554 person-years of follow-up, cataract extraction turned out to be associated with a significantly reduced risk of dementia compared with patients who didn't undergo surgery (hazard ratio: 0.71; 95%CI, 0.62-0.83; $p<0.001$) when controlling for years of education, self-reported White race, sex, age group, smoking history and stratification by apolipoprotein E genotype. They add that similar results were found even after adjusting for "an extensive list of potential confounders." To isolate cataract surgery as the main driver behind the decreased risk, they even included glaucoma surgery in their analysis and found that it didn't have a significant association with dementia risk. The researchers say they found similar results with the development of Alzheimer's dementia, as well.

The study's corresponding author, Cecilia Lee, MD, was a bit surprised by the result. "Though we hypothesized that cataract surgery would be associated with a decreased rate of dementia, we were surprised by the magnitude of the reduction," she says, "because there really is no treatment or prevention that's been reliably shown to decrease the risk of dementia."

Dr. Lee says they adjusted for many possible confounding variables to get the result. "Confounding factors are important to think about, especially in studies like this that are observational and analyze the effect of a surgery, rather than randomized, in which some people go to surgery and some don't," she explains. "One big possible confounder to consider is 'healthy patient' bias; for instance, if patients are really sick, such as

(Continued on p. 14)

RISK OF ALL-CAUSE DEMENTIA[1]



Cecilia Lee, MD; *JAMA Internal Medicine*

LETTER TO THE EDITOR

To the editor,
I read your comments on the Editor's Page in the November 2021 edition of *Review of Ophthalmology* with interest. You cited that among AMGA physicians surveyed 22 percent of respondents stated that they would stop accepting new Medicare patients. I am wondering what the statistics look like among ophthalmologists. My guess is the bulk of ophthalmologists will remain as Medicare providers and somehow endure another significant cut to payment. But why are they willing to do this? As a committee member of OPHTHPAC at the AAO, I am incredibly disappointed by the lack of engagement by AAO members in wanting to communicate to Congressional members and also contribute to the PAC. I live in an "oil town," and I can tell you the participation rate to the American Petroleum Institute by all levels of employees in contributing to their PAC is very, very high. So why do doctors who derive the bulk of their funding from Medicare not participate in the crafting of Medicare funding? It makes no sense at all to me.

Steve Orr, MD
Findlay, Ohio

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How to Get the Best People for Your Board

MATTHEW CHAPIN
Andover, Mass.
PHILIP GIOIA
Avon by the Sea, N.J.

There's an old business adage, "Investors invest in the team." In many cases, a company's initial "team" consists of the founder(s) and immediate operational team, the scientific advisory board (SAB), and board of directors. Because this team is so crucial, it's critical for the founder(s) to plan carefully before they begin recruiting team members. Here, we'll share key board-building strategies gleaned from years of working with start-ups, spin-outs from academia and company founders.

The founder(s) may be a scientific founder from academia, a practicing physician, a seasoned industry veteran, or all of the above. Founders should surround themselves with individuals that bring expertise to fill any gaps and help expand the founders' network and ecosystem. This may involve bringing in expertise in technical, regulatory, development, commercial, finance, licensing, partnerships, etc. While early-stage founders may not yet have a fully developed and functioning board process, by the time they're bringing in formal investors—whether angels, family offices or institutions—the presence of an SAB and board of directors will generally be expected. Even though investors may be angels, "friends-and-family," family offices or foundations with an emotional connection to your lead program (e.g., an investor may be a patient with that specific disease), they may not have product development or business background in pharma/bio-tech. However, in order to recognize their early financial support, you may consider offering board-observer (non-voting) rights to such an investor, so that full voting seats are held for individuals with specific backgrounds that fill any gaps in the range of expertise noted above that complement the founder(s).

At this juncture, some of the key elements for the founder(s) (one of which may be the CEO at this stage) to have a handle on include the following:

- key product differentiation;
- the technology;
- the patent situation and strategies related to that;
- development considerations;
- the market landscape;
- the key industry exit/license partners;
- how to to discuss important milestones for value inflection and financing; and
- what to expect from the initial seed funding and for the first equity financing, Series A.

Even a seasoned veteran may not have all these boxes checked completely, and early partnership with the SAB and board of directors will ensure that the CEO has a full complement of skills and talents around them to manage these concerns when coming out of the gate.

You may have to talk to a lot of people. Start with your contacts, and focus on names that will help raise credibility for your venture.

The selection process on both sides will hinge on such factors as potential conflicts of interest, other time commitments, stage of the development program, specific things asked of the board members at that particular time and the candidates' areas of expertise and overall cultural fit. Have a thick skin and don't take things personally, since there may be people who simply can't join the board, aren't a good fit or feel your company isn't right for them to contribute to. Whatever happens, stay focused on surrounding yourself with a world-class team for both the SAB and board of directors.

Independent Board Directors

The board of directors is established to represent the investors, and the CEO reports to the board. At the founding stage, a general approach would be to have at least one strong independent director, along with the CEO, major investor(s) and the founder (if separate from the CEO). There may be times that the founders reach out and identify their first independent director, but that individual may accept conditionally, requesting to see the next funds raised or second independent director join. This is their way of saying, "I'm interested, but I want to see where this goes before I fully commit and get exposed." In this case, you can consider bringing that person on to start as a consultant to engage them to support, while they feel things out.

The focus of the board of directors is strategy and broader issues. The board supports the founders and CEO on strategy for driving value inflection and decision-making. For example, is the company a single-product or portfolio company? Is it based on a specific platform or open to other products? Will the company license other assets? The board should help with high-level strategy of indication selection. There may be an indication for rapid and lower-risk proof of concept, versus what the lead commercial indication will be to build value, not to mention intellectual property issues, how much to spend, and the approach for the expensive national roll out of patents. The board of directors needs to approve the overall strategy, the outline of key milestones for seed and Series A, and the support strategy for the allocation of funds when decisions must be made about which activities to spend on.

While you may choose to engage the SAB members more on an individual level *(see below)*, your board of directors must be able to work well together. Have the members worked together in the past? Typically, those at the top of the class are desired and/or already engaged by other companies. While it may be very enticing to have the top names, you do need to ask those individuals how many other boards they're on, with what level of engagement, and whether they have the bandwidth to provide the focus for board meetings and support between board meetings that you're looking for. Be realistic, whether you're looking for a name for the slide deck or a highly functioning individual who'll serve as a part-time member of the executive team with

weekly engagement.

Note that you may not be able to address all potential future needs up front with the board makeup. Focus on the critical issues first as an early start-up. For example, commercial issues may come later, but perhaps the key issue at start-up is licensing. It'll certainly be financing and establishing and maintaining proper governance, etc. Thus, finance and legal/business development may be the key skill sets you want to focus on first. This, of course, can also be handled via simple consulting engagements, and you don't necessarily need to engage all your experts on the boards. However, be sure to think strategically about the type of board makeup that'll add the most value to you and how it will change over time. Its makeup can evolve with the company, so that the start-up isn't creating too large a board at the beginning. Again, it's a matter of what's right for a particular start-up's situation.

The Scientific Advisory Board

The goal is to be ready for your financing road show and ultimately the Series A. Surround yourself with and leverage the best expert input from your SAB so that you're ready with your plans. There are a range of issues and questions spanning regulatory, development, drug delivery, clinical, basic science, business development, etc. The profile you bring into your SAB depends on the need at that time to complement and supplement the skills and experience of the founder(s). SAB members may also play a critical role in fundraising, if investors ask to engage them as part of diligence.

You may decide to meet with the SAB as a group or continue with one-on-ones. These may be ad hoc, monthly, quarterly or annual communications. It's up to the founder(s) to set a strategy, and it depends on the start-up's needs and the most effective way for the founding CEO to engage with the SAB to extract the most value.

Tips for the Process

Factors that help ensure success include:

• *Strong board setup.* Set up your boards to provide the most valuable input and be most effective. This starts with good preparation and includes frequent communications, updates and engagement. It may seem obvious, but a meeting agenda sent out the night before, giving board members limited time to prepare, isn't effective. Make it standard practice to send out a detailed background and agenda in advance, and set the expectation that board members should review the material and come prepared. The CEO should come to the board with recommendations and leadership, not simply wait for the board to decide what to do. Having one-on-one engagements with board members between formal meetings is important as well, so the team isn't just managing things from meeting-to-meeting.

• *Effective use of sub-committees.* Balance the level of technical data at board meetings so the focus can be on strategy and key decisions. As strategic or business issues come up that are the focus of a board meeting, use sub-committee meetings with those who have the most relevant expertise on the technical topics to dive deeper off-line. The sub-committee meetings can be summarized at future board meetings or in other board communications.

• *Finance.* Particularly in the early stages, when a single-vendor activity may provide a large part of the cash on hand, focus on use of cash, runway left and presenting the scenarios of different activity plans, different financing milestones, etc., and how that drives timing

(Continued on p. 14)

To treat ocular inflammation and pain following ophthalmic surgery or ocular itching associated with allergic conjunctivitis.

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DEXTENZA is a corticosteroid indicated for:

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- The treatment of ocular itching associated with allergic conjunctivitis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

WARNINGS AND PRECAUTIONS

Intraocular Pressure Increase - Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be monitored during treatment.

Bacterial Infections - Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

Viral Infections - Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections - Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Delayed Healing - Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

Other Potential Corticosteroid Complications - The initial prescription and renewal of the medication order of DEXTENZA should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

ADVERSE REACTIONS

Ocular Inflammation and Pain Following Ophthalmic Surgery

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%), intraocular pressure increased (6%), visual acuity reduced (2%), cystoid macular edema (1%), corneal edema (1%), eye pain (1%), and conjunctival hyperemia (1%). The most common non-ocular adverse reaction was headache (1%).

Itching Associated with Allergic Conjunctivitis

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: intraocular pressure increased (3%), lacrimation increased (1%), eye discharge (1%), and visual acuity reduced (1%). The most common non-ocular adverse reaction was headache (1%).

Please see adjacent Brief Summary of full Prescribing Information.

*93% (187/201) DEXTENZA patients were satisfied with the insert in the Phase 3 Study for the treatment of ocular inflammation and pain following ophthalmic surgery.[3]

†73.6% of physicians in Study 1, 76.4% in Study 2, and 79.6% in Study 3, for the treatment of ocular inflammation and pain following ophthalmic surgery, rated DEXTENZA as easy to insert.[2,5]

References: 1. DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2021. **2.** Tyson SL, et al. *J Cataract Refract Surg*. 2019;45(2):204-212 [erratum in: 2019;45(6):895]. **3.** Data on File 00837. Ocular Therapeutix, Inc. **4.** Sawhney AS, Inventors, et al. Incept, LLC, Assignee. Drug Delivery Through Hydrogel Plugs. US Patent 8,409,606 B2. April 2, 2013. **5.** Walters T, et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11.

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FEATURES

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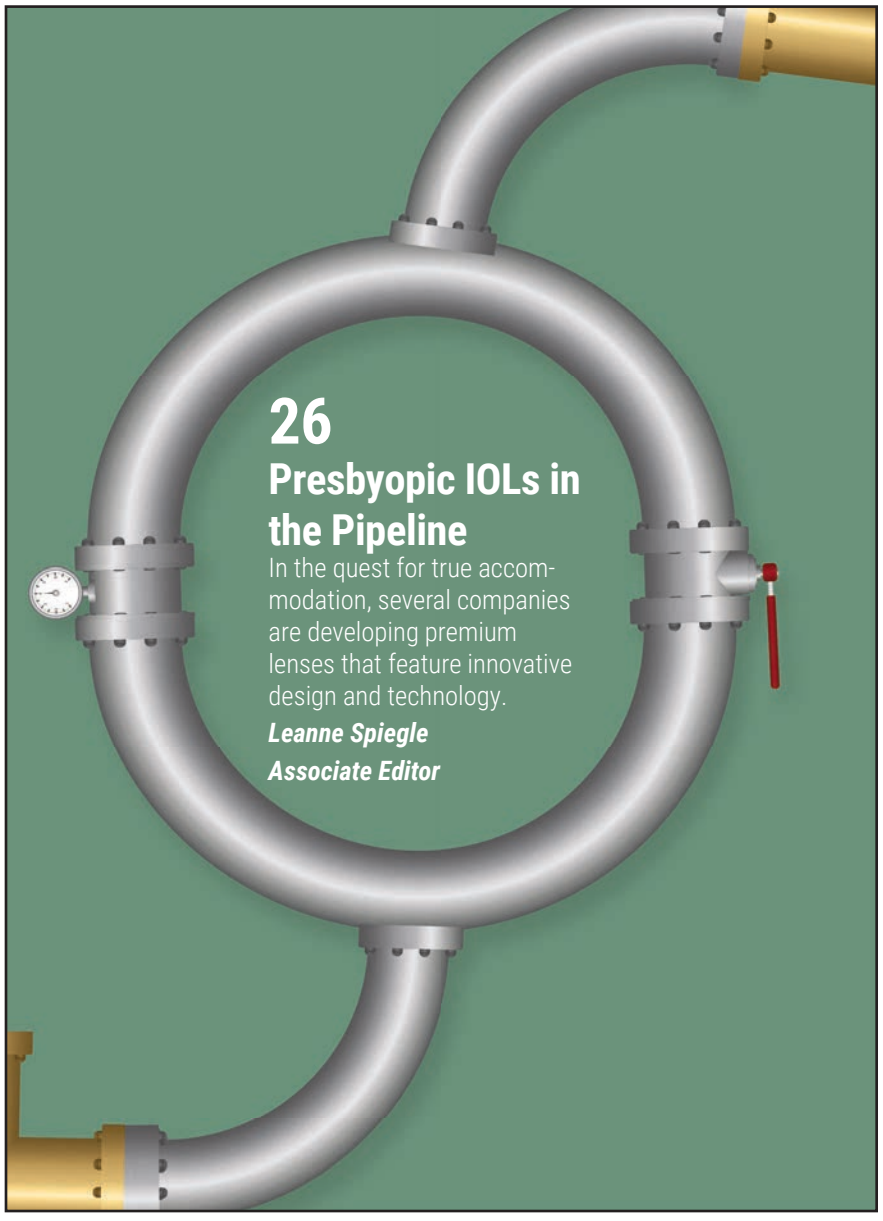

DEPARTMENTS

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INDICATION FOR USE. The iStent *inject*® W Trabecular Micro-Bypass System Model G2-W is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma. **CONTRAINDICATIONS**. The iStent *inject* W is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent *inject* W is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent *inject* W have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents. **ADVERSE EVENTS.** Common postoperative adverse events reported in the iStent *inject*® randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent *inject* vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

GLAUKOS

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Governmental Waste Is For the Birds

For years, politicians such as former Senators William Proxmire and Tom Coburn have highlighted government waste in a satirical way. For the past several years, Kentucky Senator Rand Paul has published a similar list, titled "The Festivus Report," (a reference to a fictional holiday on the sitcom Seinfeld), that lists instances of fraud and wasteful spending as a nod to the holiday's ceremonial "airing of the grievances."

In a year in which CMS has asked for increased budget from Congress so it can bear down on physicians and more actively go after fraud, one would hope the government would approach all of its other branches with such zeal. If they did, they might have been able to avoid some of the following Festivus Report doozies:

- As part of the Paycheck Protection Program—instituted to help people get through the initial waves of the pandemic—the Small Business Association paid out $4.29 billion in loans to individuals who actually weren't eligible to receive the loans or who received duplicate loans.[1] Just over $3.6 billion went to people who were already on the Treasury's Do Not Pay list (which includes those already convicted of fraud)![2] Also, nearly $700 million went to people that had already received PPP loans; the SBA didn't actually check it's own list of recipients.

The main take away from this is that the SBA <u>really</u> doesn't like checking lists.

- The NIH gave a college in Oregon $465,000 to observe pigeons playing slot machines.[3] Now, the responsible part of my brain says this is a waste of money that could have been put to a better use, but my lizard brain wants to see pigeons hitting the slots. Did they arrive in a little pigeon bus from the pigeon senior center?
- In 2015, the master detectives at the Social Security Administration sensed something was amiss: Their SS rolls showed they had 6.6 million recipients over age 112. The problem was, there were only 42 people in the world that old.[4] The issues didn't end there. In 2021, the Office of the Inspector General discovered that the SSA made nearly $4.2 billion in overpayments that may not be recouped until 2049.[5] The Festivus Report notes that the SSA deleted and can't account for more than $1.2 billion due to an error in the system.[5] On the bright side, maybe the SSA can get in on some of the better computers CMS is asking for in 2022.

Here's wishing you a happy, healthy, fiscally-responsible New Year. Now, if you'll excuse me, I've got to ask a pigeon who he's got in the second race at Belmont.

— Walter Bethke
Editor in Chief

1. SBA Inspector General. Paycheck Protection Program loan recipients on the Treasury's Do Not Pay List, Report 21-06," Page 2, SBA Inspector General, January 11, 2021.
2. U.S. Department of the Treasury Bureau of the Fiscal Service, "Do Not Pay Fact Sheet." https://fiscal.treasury.gov/files/dnp/DoNotPayFactSheet.pdf.
3. Hackenberg T. An animal model of gambling in a laboratory-based token economy. NIH Grant Project Number 1R15DA050178-01. https://grantome.com/grant/NIH/R15- DA050178-01.
4. The Associated Press. Social Security Records Show 6.5 Million Americans are Aged 112. https://www.theguardian.com/money/2015/mar/16/socialsecurity-millions-americans-aged-112.
5. The Social Security Administration Office of the Inspector General. Audit report: Overpayments with recovery agreements that will extend beyond 2049." Report A07-19-50775, p. 3. https://www.oversight.gov/sites/default/files/oigreports/SSA/07-19-50775.pdf.

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Board Selection

(Continued from p. 7)

and size of value inflections. You may come prepared with, "Option A: If we do this program first…. and Option B: If we do both…. and Option C: If we put one on the backburner," showing how each may drive different valuations on different timelines.

The founder(s) need to set the vision and culture, and to find the best team that shares the same. As one example, there may be times—especially during seed and bridge rounds—that the operations/management team may need to take a decrease (or stop) in salary. Will the team you recruit be on the same page? Each member of the board of independent directors and SAB will have a critical role in your success by providing specific expertise. The best leaders will be humble and will closely examine their own areas in which they need support so they can identify the ideal profile of the board members. Carefully plan your approach to creating and managing your boards, and you'll see how a specifically selected, highly-functioning board is key in driving the company forward.

Suggested Reading:
1. Booth B. Atlas Ventures. https://lifescivc.com/2012/03/high-performing-boards-in-early-stage-biotech/.
2. Kolchinksy P. The Entrepreneur's Guide to a Biotech Start-Up, 4th Ed. https://www.ctsi.ucla.edu/researcher-resources/files/view/docs/EGBS4_Kolchinsky.pdf.

Mr. Chapin is a senior vice president of the Asset Development & Partnering Group at Ora. The company offers drug, biologic and device consulting; preclinical and clinical research execution; and regulatory and development strategy to support its clients and partners. Mr. Gioia is CEO and co-founder of Vinci Pharmaceuticals, focused on developing products to fill unmet needs in retina. He has several other board positions within ophthalmology and is managing director of consulting firm PharM&A Advisors. Send comments or questions to mchapin@oraclinical.com or visit

Cataract Surgery and Dementia

(Continued from p. 3)

when they just had a stroke or heart attack, then poor vision isn't on the top of their list of things to deal with, so they're unlikely to undergo cataract surgery. On the other hand, people who are healthy and/or health-conscious are more likely to get cataract surgery if their physician recommends it—in other words, maybe the patients in your study who could go for cataract surgery were healthier at baseline. However, since the ACT study patients are members of Kaiser Permanente Washington, we could access all of their medical records, so those confounders could be adjusted for in the analysis. Despite them, we found strong associations with cataract surgery and decreased dementia risk."

There are different theories regarding the mechanism behind cataract surgery's association with dementia. "A common hypothesis is that, when you remove the cataract and your vision gets better, there's more and better visual stimuli, which may increase the stimulation of the brain, which could be protective," Dr. Lee says. "Another idea is that, as your vision gets better, you're better able to engage with the world. This means that you're more likely to socialize, go for a walk, be less depressed, drive at night, etc. These psychosocial risk factors are known to be associated with dementia risk; they may be improved secondary to having improved vision. The third theory involves a concept called 'cognitive overload,' that states there are different loads of stimuli from different sensory systems. If the brain receives a very poor signal from vision, the theory explains, it spends a lot of energy to try to understand the poor visual signals and that confuses and overwhelms the brain.

"The theory that's most interesting to me," Dr. Lee continues, "has to do with blue light. As you know, when we develop cataracts as we age, the lens becomes yellow, which is especially good at filtering out blue light. There are cells in the retina called IpRGC, or intrinsically-photosensitive retinal ganglion cells, that are known to be involved in circadian rhythms and cognition. There are some reports of Alzheimer's being associated with those cells, which are sensitive to blue light. So it's possible that improvement in the quality of light, including blue light, that enters our retina after cataract surgery, might awaken those cells." ◀

1. Lee C, Gibbons L, Yee A, et al. Association between cataract extraction and development of dementia. JAMA Intern Med. doi:10.1001/jamainternmed.2021.6990 Published online December 6, 2021.

Update: Monitoring Glaucoma at Home

As technology improves, self-monitoring by patients is becoming feasible.

CHRISTOPHER KENT
SENIOR EDITOR

It's no secret that having patients monitor their own eye-disease-related parameters is on the horizon. It's also no secret that COVID-19 and the resulting restrictions in office visits caused a significant acceleration of that trend.

To learn more about the current status of this shift, we spoke to an ophthalmologist who is well-versed in this technology to find out how close we are to having home monitoring be an everyday reality.

Shifting the Focus

Lama A. Al-Aswad, MD, MPH, who practices at NYU Langone Health in New York City, is a professor of ophthalmology, a professor of population health, and the director of teleophthalmology, artificial intelligence and innovations at the NYU Grossman School of Medicine. She worked on the possibility of patient remote screening and monitoring for a number of years prior to COVID, but says the opportunity to really move forward with home monitoring came when the pandemic hit. "We were already experimenting with things like the iCare Home tonometer," she says. (The iCare Home is a rebound tonometer that patients can use on their own eyes without the need for a topical anesthetic. To learn more, see "IOP Around the Clock: How Close Are We?" in the June 2018 issue of *Review*.) "We wanted to better understand how well a device like that works in real-world use, and whether it has a place in our practice.

"As part of my research I was sending the iCare device home with patients, free of charge—especially in cases where I was suspicious about the status of the patient's glaucoma," she continues. "I'd usually ask patients to check their pressure six times a day, which produced a lot of information, some of which was surprising. There were times when I was shocked by a patient's data when I got the device back. Some had multiple IOP elevations at times of day when they weren't in my office.

"Then COVID happened, and everything changed," she says. "In our practice, with the infrastructure available at NYU, we launched virtual patient visits using videoconferencing; we were up and running within two weeks of the government easing the restrictions on telemedicine reimbursement. We did more than 1,500 virtual visits over the next four months. This quickly increased the urgency of the question: How can we do a better job of evaluating vision remotely? I created a checklist for our practice listing the visual parameters we needed to be evaluating and how we might go about performing these visits."

Checking Acuity at Home

Dr. Al-Aswad says the first two glaucoma-related factors they wanted to focus on assessing were visual acuity and IOP. "Initially, some people thought that sending a visual acuity printout, along the lines of the Amsler grid, might be a workable way to check visual acuity," she says. "The problem is that you don't know what the patient is doing with it. We decided that a digital app that could be used on a computer or smartphone would be a better approach.

"We quickly discovered that the existing apps weren't ideal," she continues. "First of all, we wanted an app that we could connect to our electronic health record system.

Home monitoring of IOP and visual fields can be done using devices like these. Proponents say the data has been shown to be clinically useful, and that most patients have been enthusiastic about the experience.

This article has no commercial sponsorship.

Dr. Colvard is a surgeon at the Colvard-Kandavel Eye Center in Los Angeles and a clinical professor of ophthalmology at the Keck School of Medicine of the University of Southern California. **Dr. Charles** is the founder of the Charles Retina Institute in Germantown, Tennessee.

Leonard Seibold, MD

These IOP measurements made by a patient before and after a repeat selective laser trabeculoplasty treatment illustrate a key advantage of multiple daily measurements. If in-office measurements had been taken at the time point shown by the arrows, a clinician might have concluded that the treatment didn't lower the pressure significantly. However, with multiple home measurements, the mean pressure was shown to have dropped from 22.8 mmHg pre-treatment to 18.5 mmHg post-treatment, a 19-percent reduction.

Second, we noticed a challenge with these apps: the patient's ability to zoom in and enlarge an image. If the patient can zoom in on your image, you're going to have a hard time getting useful information about the patient's visual acuity. For that reason, we decided to develop an app of our own. We began by creating a quick-and-dirty app in our lab called 'Snap-eye,' that doesn't allow patients to alter the size of the test images. Once we had that in hand, we reached out to our institution and showed them what we'd done. We asked to create a more robust build, and connect it to EPIC, our electronic health record system.

"Ultimately," she explains, "we created two versions of the app: one that can connect to our EHR, and a free-standing version that's available for download at no charge at the Google Play store and the Apple App Store. We thought it might be something other ophthalmologists could use, especially during COVID. Our in-house version of the app allows patients to check their vision while waiting in the virtual waiting room during a virtual visit. The resulting data directly populates to our EHR.

"Since developing the app, we've validated it with 120 patients," Dr. Al-Aswad notes. "Our study showed that it's very accurate in patients with good vision, but somewhat less accurate when evaluating patients with worse vision—a common problem with apps designed for this purpose. We're currently getting ready to publish that data. In the meantime, we're working on other apps for similar purposes."

IOP and Visual Fields

Regarding home-checking of IOP, Dr. Al-Aswad notes that COVID made it impossible to bring patients into the office for training in how to use the iCare device. "We created a virtual training visit," she says. "We'd send the patient the device; they'd open it and then have a virtual training visit with the technician. They'd keep the device for a week, checking their pressure six times a day, and then mail it back to us.

"We did charge patients for that, to cover the cost of the device, the cost of shipping the device back and forth, and the cost of training," she continues. "After we got the data back, we'd do a virtual visit with the patient to discuss the data and how their management would or wouldn't change. The patients really liked this system. In fact, we had a wait-list of patients wanting to use the device, and we purchased an additional 10 devices to help meet the demand."

Dr. Al-Aswad notes one issue they had with the iCare tonometer: They couldn't plug the data directly into their EHR. "One of the NYU medical students in my lab, Jaideep Prasad, built an analog-to-digital connector for the iCare device," she says. "Without that, we could only access the tonometry data on the iCare website; then we'd have to input the data manually or scan it into our EHR. With a digital connection, the data goes directly into our research electronic data capture, REDCap."

Another key piece of information Dr. Al-Aswad wanted to collect was visual field data. "Prior to COVID we acquired virtual-reality visual fields to try using it for screening as part of our teleophthalmology mobile unit," she says. (Virtual visual fields involve the use of goggles and oculokinetic perimetry, in which the patient's eye moves to focus on changing stimuli, rather than remaining focused on a central point. To learn more, see "Checking Visual Fields Using Virtual Reality" in the March 2021 issue of *Review*.) "We thought, why not just send them to patients' homes and let them do the testing?

"It took a while to get approval for this, and then do training and so forth," she acknowledges. "Once we had that, we ran a small pilot study as a summer project for two of our NYU medical students, Galen Hu and Jaideep Prasad, to investigate the feasibility and acceptability of virtual-reality visual fields and the iCare Home when used by patients at home, and to validate their accuracy. We trained the patients in the office, then did a virtual training with them after they received the devices, and after using the devices they sent them back. The data produced by the virtual reality devices was clinically significant. Based on

the data we got, I saw some patients sooner than we'd planned. Meanwhile, the response from patients was amazing; those who took the devices home loved them. Some said they liked doing the virtual visual field more than the Humphrey visual field. Similarly, 42 percent of these patients liked using the iCare Home device more than undergoing Goldmann in the office.

"At this point," she notes, "it's feasible to have patients monitor their own visual acuity, IOP and visual field at home."

Retinal Imaging and OCT

Two more data points that would clearly be helpful are optic disc photos and optical coherence tomography scans. "Right now, patients taking their own retinal photos is theoretically possible, but it's not easy to do," Dr. Al-Aswad says. "With the current technology you need to have an experienced user and you have to dilate the pupil to get a good image, although some systems claim that dilation isn't necessary. The bottom line is that it's still early for this technology—but it will become more practical soon. I've also been looking at patient-performed OCT. It's still in development and the cost is prohibitive, so it's not going to be available to everybody for home use."

Dr. Al-Aswad points out that technological advances, including artificial intelligence, are already suggesting new ways to obtain the kind of information OCT devices can reveal. "Felipe Medeiros published a study showing that you can train an AI algorithm to evaluate the optic nerve and predict nerve fiber layer thickness from a disc photo using machine-to-machine learning," she says. "Maybe instead of home OCT, the future will include using AI to derive data like retinal or nerve fiber layer thickness from patient-captured images of the retina and optic nerve."

One other practical issue also needs to be resolved: getting reimbursed when working with patients who are doing home monitoring. "Most remote-monitoring reimbursement codes are somewhat problematic because they're not specific for ophthalmology," she points out. "These codes were not created with high-cost devices—such as the ones used in ophthalmology—in mind. For example, the current codes require that the patient use a device more than 20 days a month. If you give a patient one of these devices for 20 days, you won't recoup the cost of the device for a few years. Sometimes we use the codes in our practice, but we always get prior authorization from the insurance company.

> **Patients monitoring their own eyes is definitely going to happen. It's only a matter of time.**
>
> ***—Lama A. Al-Aswad, MD***

"The other economic approach we found that made this work during COVID is to charge patients a flat fee to take the device home for a week," she says. "With this system, you might recoup the cost of the device quicker just because you're not asking the patient to keep it for 20 days. Theoretically, you can send the device to a different patient every week."

Empowering Patients

"Part of the reason for my interest in home monitoring is that I believe patients need to be empowered to take care of themselves," Dr. Al-Aswad says. "Although I've been a glaucoma specialist for 18 years, I hadn't really thought about this until one of my patients said to me, 'Doctor, I feel powerless between visits. I wait three to six months to see you, and I don't know if I'm stable or getting worse. I need to have some power over my glaucoma.' That opened my eyes. If patients have blood pressure problems or diabetes, they can measure their blood pressure or blood sugar between visits. But with glaucoma you can't do anything between visits.

"Patients monitoring their own eyes is definitely going to happen; it's only a matter of time," she continues. "The technology we have today for accomplishing this is OK, but new technologies on the horizon will be even better. Right now, for example, companies are creating implantable devices that can measure IOP. One of them is already approved in Europe, and it's only a matter of time before they're available in the United States. Imagine being able to continuously monitor your IOP through your smartwatch, to see if there are changes that need to be addressed."

Dr. Al-Aswad points out that patients are likely to be the biggest beneficiaries of the shift to home monitoring. "We don't take into consideration how much time and effort regular office visits cost the patient," she notes. "Yes, many of our patients are elderly and retired, but not all of them are, and even those who are retired may find these office visits challenging to manage. We need to respect the patient's time and reduce the need for visits to our offices. And, we need to remember that our patients often feel powerless between visits.

"Home monitoring will address all of this," she concludes. "We'll be better able to understand and control the disease because we'll have better data. Patients won't have to give up so much time coming to our offices. And patients will finally feel that they have some control over their disease.

"This is the future," she adds, "and it's not far off." ◂

Dr. Al-Aswad reports no financial ties relevant to the article.

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DME.

375 MATH TESTS

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

REGENERON

EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

Demonstrated efficacy outcomes in VISTA and VIVID, phase 3 anti-VEGF trials in DME (N=862)[1]

Mean change in BCVA (ETDRS letters) at Year 1 from baseline[1-5,*]

	Initial Gains (Month 5)		Primary Endpoint (Year 1)		Prespecified Exploratory Endpoint (Year 3)	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
EYLEA Q4	+10.3 (n=154)	+9.3 (n=136)	+12.5 (n=154)	+10.5 (n=136)	+10.4 (n=154)	+10.3 (n=136)
EYLEA Q8†	+9.9 (n=151)	+9.3 (n=135)	+10.7 (n=151)	+10.7 (n=135)	+10.5 (n=151)	+11.7 (n=135)
Control	+1.8 (n=154)	+1.8 (n=132)	+0.2 (n=154)	+1.2 (n=132)	+1.4 (n=154)	+1.6 (n=132)

P<0.01 vs control at Year 1.

The analyses of these exploratory endpoints were not multiplicity protected and are descriptive only.

Year 2 data was consistent with results seen in Year 1.[5]

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled clinical studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received: 1) EYLEA 2 mg Q8 following 5 initial monthly doses; 2) EYLEA 2 mg Q4; or 3) macular laser photocoagulation (control) at baseline and then as needed. From Week 100, laser control patients who had not received EYLEA rescue treatment received EYLEA as needed per re-treatment criteria. Protocol-specified visits occurred every 28 (±7) days.[1]

In both clinical studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52, as measured by ETDRS letter score.[1]

*Last observation carried forward; full analysis set.
†Following 5 initial monthly doses.

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anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology.* 2014;121(11):2247-2254. doi:10.1016/j.ophtha.2014.05.006 **3.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **4.** Data on file. Regeneron Pharmaceuticals, Inc. **5.** Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. *Ophthalmology.* 2016;123(11):2376-2385. doi:10.1016/j.ophtha.2016.07.032

Please see Brief Summary of Prescribing Information on the following page.

04/2021
EYL.21.03.0211

EYLEA® (aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.2 Increase in Intraocular Pressure
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

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

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

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

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

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

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

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

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

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

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

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

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

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019
EYLEA® (aflibercept) Injection full
Prescribing Information.

EYL.20.09.0052

Buckets of Obligations

Musings on life, ophthalmology and the practice of medicine.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

It's become a tired cliché, but the concept still rings true: The bucket list, a list of the goals, experiences and dreams you want to fulfill—as if life were only a matter of crossing things off a list. So, you cross everything off and then what? You're dead? That's no prize. Or, maybe you get to the end of the list and just find more stuff to add to it. In that case, life becomes a process, rather than a life lived. However, as ordered creatures, it's natural to think about our lives as moving from activity to activity, like bed to work, breakfast to lunch, etc., from one project or goal to the next. We like to take stock, or even pride, in what we have accomplished.

Most often bucket lists involve places to visit or activities that we'd like to do but haven't allocated either the time or resources to do them, like visiting Paris or skydiving. There's a somewhat current Facebook meme that gives you a point for each activity you've accomplished, and it's a popular way to see how you compare to your friends; it's silly entertainment, trivializing your life.

On a more considered and serious note though, most of us have an internal list of our life's goals, the things we want to achieve for ourselves and our families before we kick the proverbial bucket. Get a degree, a job, financial security, children, grandchildren, a sports car. OK, that last one was all me. But seriously, as I've gotten older, I'm starting to keep tabs on how well I'm marching past my line of goalposts. I think I'm tying it all together pretty well. At this later point in my life, I've got a lot to look back on with a fair degree of satisfaction. I don't really have much left to prove or resolve. I know this sounds like bragging, and I guess it is, a little. But it's a nice feeling. More importantly, however, it's allowing me to take a different path, to do things I've not had the time or flexibility to do, things that I couldn't do because I had obligations. I had the obligation to provide for my family, my patients, my practice, and to just about everyone and everything, it seemed. This isn't to say I haven't enjoyed my life; I have very much. But it's different for me now.

Getty Images

To a degree, the weight has been lifted, and I'm finding myself approaching each day with a lighter step and less worry. It's freeing and it's fun to not have to engage with serious concern for what the future holds, but instead to simply go and do. In my younger days I was intense. Everything mattered—a lot. And, I felt success was hard-won. This approach worked, but took its toll. So, at this stage, after looking back at all the items on my list that have been accomplished and the milestones achieved, I can give a sigh of relief, a relaxing of my shoulders and perhaps even a small smile. It feels a bit weird, but a good weird. I'm getting to like it. And, surprisingly, those around me seem to notice and like it to.

At the risk of being morbid, I think I've gotten to this better place because to a large degree my life's work has been accomplished. Now everything that follows is gravy—doing what I want to do, without the Sword of Damocles over my head. I can proceed with a quiet sense of both closure and new horizons. I hadn't really expected this. And maybe I could have had it a lot sooner if I had taken a different approach to life. But I'm pleased I'm here at this point at all. Now, instead of feeling like I have obligations, I have opportunities. To do new things, to enjoy my life and to finally have an empty bucket. ◀

This article has no commercial sponsorship. **Dr. Blecher** is an attending surgeon at Wills Eye Hospital.

PAUL M. LARSON, MBA, MMSC, COMT, COE, CPC, CPMA

MEDICARE Q&A

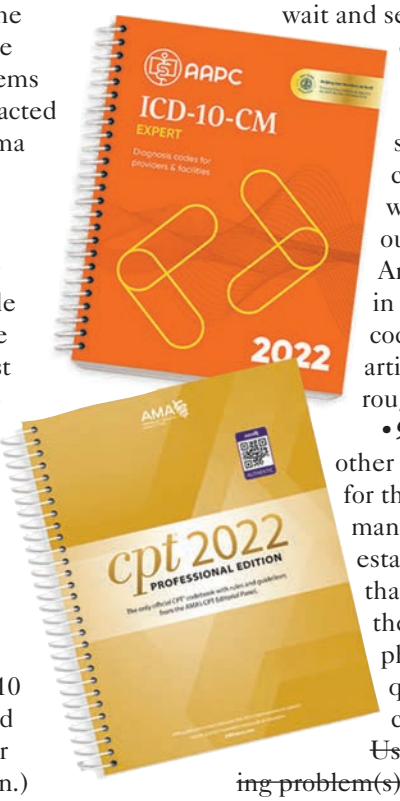
Medicare: What's New For 2022

Important changes to different levels of CPT codes, Medicare reimbursement, MIPS and rules for facilities.

This year we have some new CPT Category I and Category III codes effective for use in eye care on January 1, 2022. We also have changes to several codes. The impact of the Medicare Physician Fee Schedule especially seems to have negatively impacted payment in the glaucoma laser and surgery area.

While Medicare has reduced the values on many of our commonly used codes, it is possible Congress will act in late December or in the first part of the year to mitigate some of the cuts—so reimbursement values might rise after this article is published (they shouldn't go down any further, though).

(Note: There aren't many updates to ICD-10 for eye care in 2022, and we covered those in our November 2021 column.)



Q What are the CPT Category I code changes that go into effect on January 1, 2022 that might affect eye care?

A In terms of exam coding, last year we had a momentous change to E/M coding. Though the effect of that change remains, we'd all like to see a bit more clarity in some circumstances; but we'll have to wait and see. The Eye exam codes remain unchanged for coding. 99211 had a small change in the code descriptor, but we'll see if it turns out to be significant. Any words deleted in the language for codes shown in this article are in strikethrough text:

• ***99211*** Office or other outpatient visit for the evaluation and management of an established patient that may not require the presence of a physician or other qualified health care professional. ~~Usually, the presenting problem(s) are minimal~~

In terms of new codes, we have three of import and a fair number of changes to code descriptors. The new codes are:

• ***68841*** Insertion of drug-eluting implant, including punctal dilation when performed, into lacrimal canaliculi, (each)

The above code has a parenthetical instruction to report the actual drug-eluting implant separately.

• ***66989*** Extracapsular cataract removal w/IOL insertion, complex; with insertion of intraocular (e.g., trabecular meshwork, supraciliary, suprachoroidal) anterior segment aqueous drainage device, without extraocular reservoir, internal approach, one or more

• ***66991*** Extracapsular cataract removal w/IOL insertion; with insertion of intraocular (e.g., trabecular meshwork, supraciliary, suprachoroidal) anterior segment aqueous drainage device, without extraocular reservoir, internal approach, one or more

Both 66989 and 66991 are combination codes (they take two codes and combine them into a single code). In 2022, the pair only apply to devices such as iStent or Hydrus and there are some important Category III code changes that accompany them. Note also that you will no longer be able to code for more than one device or device insertion as that is baked into the new codes. The revised codes are:

• ***67141*** Prophylaxis of retinal detachment (e.g., retinal break, lattice degeneration) without drainage, one or more sessions; cryotherapy, diathermy

• ***67145*** Prophylaxis of retinal detachment (e.g., retinal break, lattice degeneration) without drainage, one or more sessions; photocoagulation

• ***92065*** Orthoptic and/or pleoptic training, with continuing medical direction and evaluation

This article has no commercial sponsorship.

Mr. Larson is a senior consultant at the Corcoran Consulting Group and is based in Tucson, Arizona. He can be reached at plarson@corcoranccg.com.

FIGURE 1

CPT	Short Description	2021	2022
92014	Comprehensive eye exam, established	$128	$127
99204	E/M new patient level 4 exam	$170	$165
99213	Intermediate eye exam, established	$92	$89
99214	E/M established patient level 4 exam	$131	$126
66984	Cataract surgery w/ IOL	$548	$529
66174	Canaloplasty w/o retention of device	$948	$739
66183	ADD, external approach (ExPress)	$1,038	$1,002
66711	ECP w/o concurrent cataract surgery	$510	$492
67141	Prophylaxis of RD (retinal tear), cryo	$531	$265
67145	Prophylaxis of RD (retinal tear), laser	$534	$237

Q What about Category III CPT codes in 2022?

A We have three codes related to the new combination codes above; there is one new code—which has the "multiple devices" caveat as above—and two deleted codes. The new code, though valid, has the subtlety of being an off-label use of the only two valid devices, so it's not likely to be payable under coverage policies until the manufacturers can change their approved FDA labeling. The codes are:

• ***0671T*** Insertion of anterior segment aqueous drainage device into the trabecular meshwork, without extraocular reservoir, and without concomitant cataract removal, one or more

The pair of related but deleted codes:

• ***0191T*** Insertion of anterior segment aqueous drainage device, without external reservoir; internal approach, into the trabecular meshwork

• ***+0376T*** Insertion of anterior segment aqueous drainage device, without extraocular reservoir; internal approach, into the trabecular meshwork; each additional device insertion

There's not much information on what devices or material goes with the below codes at this point, but the codes are "live" nonetheless. Other new Category III codes for 2022 are:

• ***0660T*** Implantation of anterior segment intraocular nonbiodegradable drug-eluting system, internal approach

• ***0661T*** Removal and reimplantation of anterior segment intraocular nonbiodegradable drug-eluting implant

The above two codes have parenthetical notes to bill the medication separately.

• ***0687T*** Treatment of amblyopia using an online digital program; device supply, educational set-up, and initial session

• ***0688T*** Assessment of patient performance and program data by physician or other qualified health care professional, with report, per calendar month

• ***0704T*** Remote treatment of amblyopia using an eye tracking device; device supply with initial set-up and patient education on use of equipment

• ***0705T*** surveillance center technical support including data transmission with analysis, with a minimum of 18 training hours, each 30 days

• ***0706T*** interpretation and report by physician or other qualified health care professional, per calendar month

The above five codes have parenthetical notes not to bill them with CPT 92065 and a few other codes.

• ***0699T*** Injection, posterior chamber of the eye, medication

This last code goes with Dexycu, which already has an existing code valid for use (J1095).

Q I heard that there were changes to the expiration dates on a couple of drugs with pass-through status. Can you tell me the details?

A There are two eye-related codes that would have had their "Pass-through payment" status expire well before 2022 was over, but CMS noted it will extend this special privilege through 12/31/2022 in order to get another full years' data on pricing for each. Those two codes are shown below; they go with Dexycu and Dextenza, respectively:

• ***J1095*** Injection, dexamethasone 9 percent, intraocular, 1 microgram

• ***J1096*** Dexamethasone, lacrimal ophthalmic insert, 0.1 mg

I'll also comment on Omidria (J1097) here—which had its "pass-through" status expire way back in 2020 but still has its payment in 2022. As in 2021, this drug has coverage under the "Non-Opioid Pain Management Drugs and Biologicals that Function as Surgical Supplies" program.

Q What about physician reimbursement under Medicare for 2022?

A As the famous saying goes: "Aye, there's the rub." What you see in Figure 1 could change soon if Congress makes new legislation, because it's not within CMS' power to make the changes desired. As mentioned in the introduction to this month's article, the payments

FIGURE 2

CPT	Short Description	2022 Surgeon	2022 ASC
66989	Complex cataract/IOL insertion, with AC aqueous drainage device (ADD), internal approach, 1/more	$832	$3,246
66991	"Regular" cataract/IOL with ADD, internal approach, 1/more	$664	$3,246

FIGURE 3

CPT	Short Description	ASC		HOPD	
		2021	2022	2021	2022
66821	YAG Capsulotomy	$255	$261	$504	$514
15823	Blepharoplasty, Upper lid	$867	$887	$1,715	$1,749
66984	Cataract/IOL	$1,039	$1,063	$2,079	$2,121
67036	Pars Plana Vitrectomy	$1,872	$1,919	$3,918	$4,000

listed in Figure 1 might have been changed by the time you read this. So, as of this writing, those are some 2021 vs. 2022 physician payments (payment shown is for "surgeon in facility," not the office setting). Payments shown in the figure are rounded to the nearest whole dollar.

The large 67141 and 67145 payment decreases are largely because the global periods for this pair are now 10 days instead of 90. Exams for this treatment at the two-week interval would now be billable since there would be no global postoperative period in play then.

As of this writing, the 2022 payments for the new combination codes at the beginning of the article for surgeon in facility and ASC appear in Figure 2 (pg. 25).

The "Most Favored Nation" drug model for Part B drugs used in the office, that got a lot of publicity because of its onerous reimbursement provisions last year, got a stay in the Federal Courts early in 2021, and then CMS later placed it on hold. There's no mention of it in the Final Rules for the 2022 Fee Schedules at all. Despite this, there's a strong move afoot to allow Medicare to negotiate drug prices. We'll see what the details are if it passes.

CMS changed the reimbursement status of remote imaging code 92229. It was changed from "contractor-pricing" in 2021. The main issue was that there were widely disparate payments as each MAC made its own decision. The payment now has a national rate of $45.36; as with most codes, payments vary slightly based on cost-of-living differences. The code 92229 is for "Imaging of retina for detection or monitoring of disease; point-of-care automated analysis and report, unilateral or bilateral."

Q For facilities, what are the biggest Medicare changes in 2021?

A In 2021, Medicare increased the ASC conversion factor by 2 percent, and CMS increased reimbursement for hospital outpatient departments by the same amount. The prior authorization process CMS began last year for blepharoplasty, some ptosis codes and Botox injections and drugs continues for HOPDs; ASCs aren't affected. Some 2021 vs. 2022 ASC and HOPD payments appear in Figure 3.

Q What about changes to Medicare beneficiaries' obligations and other administrative changes for my office?

A The 2022 Medicare Part B deductible rose to $233 (from $203 in 2021), so you'll need to collect for this greater amount beginning in January. The revised ABN we wrote about in the September 2020 installment of Medicare Q & A may be used now but it becomes mandatory after the expiration of the Public Health Emergency declaration.

The monthly premium beneficiaries pay for Medicare Part B rose significantly, from $148.50 to $170.10 per month in 2022; we don't typically discuss it here since it is paid by our patients, but in a public comment CMS stated why, and it succinctly illustrates the problems CMS has with continually rising drug prices. CMS noted three main reasons:

- rising prices and utilization;
- Congress lowered the amount of the planned increase in Part B premiums for 2021 (and CMS is obligated to make adjustments to keep the program solvent); and
- additional contingency reserves due to uncertainty over CMS paying for Aduhelm, the controversial and very expensive Alzheimer's drug.

Q Can you summarize the changes in the Quality Payment Program or MIPS for 2022?

A Yes, and, though they're important, they're mostly related to the scores you need to get. The Quality Payment Program enters year six in 2022, and there are only modest revisions to the Merit-based Incentive Payment System that most providers use. The maximum negative payment adjustment will remain at 9 percent for the Medicare payments you get in 2024 (from reporting in 2022), though the minimum composite score to avoid a penalty increases a lot—all the way to 75 points from the 60 points needed in 2021. This change may make it far more difficult for providers to earn a bonus. On the penalty side, as in 2021, if CMS allows another MIPS Hardship Exception for COVID-19, there won't be many penalized and, since the MIPS program is budget neutral, fewer penalties means those who do well won't get as much as they might otherwise.

Exceptional Performance bonuses remain excluded from this budget-neutral calculation—but providers must achieve 89 points to get it—and 2022 is the last year for this special bonus.

In 2022, the weighting of Quality and Cost change to 30 percent for Quality and 30 percent for Cost. The weights of Improvement Activities and Program Interoperability remain unchanged. Last year, CMS put the new MIPS Value Pathways system on hold, but now it's slated to go active in 2026. Few details are available so far, and CMS notes that more information will accompany future rulemaking. ◀

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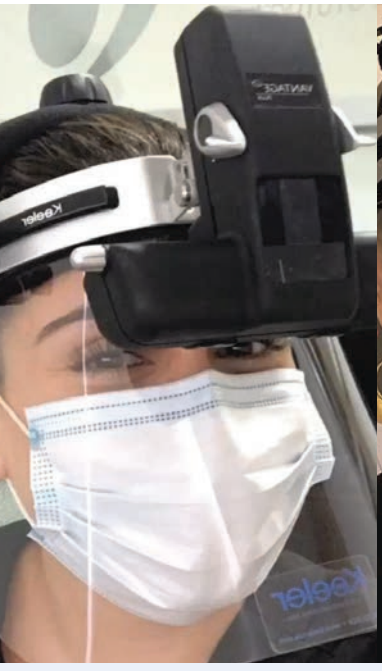


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PRESBYOPIC IOLS IN THE PIPELINE

In the quest for true accommodation, several companies are developing premium lenses that feature innovative design and technology.

LEANNE SPIEGLE
ASSOCIATE EDITOR

The very first multifocal intraocular lens to be used in the United States was the AMO Array, approved by the FDA about two decades ago. Since then, numerous companies have been designing and developing unique models of these presbyopia-correcting lenses—and even a lens-correcting laser—to broaden the number of options available to patients with varying expectations and desired outcomes. These lenses may offer presbyopes a more dynamic range of vision, and even spectacle independence in some cases.

Much of the new tech aims to reduce the negative visual effects that can occur in patients following implantation of a diffractive IOL, the most common of these being reduced contrast sensitivity and dysphotopsias (i.e., nighttime glare, halos and starbursts). Besides tried-and-true multifocal IOLs, there are several other presbyopia-correcting IOL technologies attempting to make their way into ophthalmic practice in the coming years. Here, we'll discuss where each of these presbyopic IOLs is in the pipeline, the mechanisms behind each design and what preliminary trials have demonstrated so far about their potential visual and clinical outcomes.

Trifocal IOLs

Two years ago, in the summer of 2019, the PanOptix IOL (Alcon) became the first and only trifocal IOL to date to receive FDA approval. Its advent provided a new solution for patients in search of a premium IOL with the ability to give some improvement of vision at near, intermediate and distance. Specifically, the PanOptix lens distributes half of the light for distance and 25 percent each for intermediate and near vision. Other trifocal IOLs being developed have varying percentages of light distribution.

In terms of downsides, trifocal lenses can have a negative impact on night vision as a result of splitting the light in three ways to accommodate each of the three focal points. Patients can also experience halos, starbursts and glare, as well as some reduced contrast around objects. Depending on a patient's unique goals, lifestyle and occupation, any of the following trifocal IOLs currently making their way through the pipeline may offer an expanded range of vision.

• ***EnVista trifocal (Bausch + Lomb).*** B+L is currently conducting trials on this addition to its enVista family of IOLs. The enVista trifocal will include the same features as other enVista lenses, with the added bonus of a more continuous range of vision from distance to near. The single-piece hydrophobic acrylic is currently under investigational use in the United States, and B+L is getting ready to conduct its Phase III clinical trial.

The enVista trifocal IOL, along with the other enVista IOLs, is made with what B+L calls the "TruSight" optic design, consisting of a material 25 times harder than a traditional hydrophobic acrylic lens, which the company says increases its resistance to scratches and abrasions.[1] The company adds that the lens haptics, dubbed "AccuSet," were also created to be durable and stable. B+L says the design provides lens stability and a 300 percent greater radial compression force than traditional hydrophobic acrylic.[1]

"We're currently enrolling for the enVista trifocal IOL Phase III clinical

This article has no commercial sponsorship.

Dr. Blecher was a paid investigator for Acufocus in the IC-8 IOL study. **Dr. Chu** was a principal investigator for AcuFocus IC-8 and is on the medical advisory board for Perfect Lens.

trial," says Chuck Hess, vice president and general manager of U.S. Surgical, Bausch + Lomb. "This multicenter, randomized study will include more than 500 subjects undergoing bilateral cataract surgery. Subjects will receive either enVista trifocal IOLs or enVista monofocal IOLs. Investigators will determine efficacy endpoints after six months and safety endpoints after 12 months based on post-surgical observation." Mr. Hess notes that the study is intended to support a Pre-Market Approval application filing with the FDA.

As far as potential candidates and outcomes for the enVista trifocal IOL, Mr. Hess explains that while it's a bit early to talk specifics, "Clinical trial results will allow [B+L] to determine the specific attributes of the investigational lens," and mentions that the company is developing a toric version as well. In addition to this trifocal IOL for correcting presbyopia, Mr. Hess shares that B+L is also working on several extended-depth-of-focus IOL technologies currently being researched and developed.

"The more IOLs that are available, the greater the opportunity for physicians to meet the specific needs of each individual patient," says Mr. Hess.

• ***AT LISA trifocal (Zeiss).*** Another presbyopia-correcting IOL that could be making its way into your practice is the AT LISA trifocal IOL, which is already approved for use in a number of countries around the globe. ("LISA" is an acronym that summarizes the concept behind the lens: Light distributed asymmetrically, Independence from pupil size, SMP technology (for a smooth lens surface) and Aberration-correcting optimized aspheric optic.) [2]

AT LISA trifocal

The AT LISA trifocal is made of a hydrophilic acrylic material with hydrophobic surface properties and has an optic diameter of 6 mm and a total diameter of 11 mm. The power ranges from zero to +32 D in 0.5-D increments. It requires a small 1.8-mm incision for its insertion using the company's BlueMICS 180 injector.

A study of 227 eyes of 114 patients who underwent bilateral implantation of the AT LISA trifocal found that after 12 months, outcomes for binocular uncorrected distance, intermediate and near visual acuity were ≤0.3 logMAR (20/40) in 99, 98.1 and 91.4 percent of eyes, respectively, and patients achieved normal contrast sensitivity at six months postop.[2] As for patient satisfaction, the study reports that 12 months after surgery, 93.3 percent, 89.4 percent and 84.6 percent of patients were satisfied or very satisfied with their distance, intermediate and near vision, respectively.[2]

To reduce the most commonly reported negative effect of diffractive IOLs, dysphotopsias, Zeiss designed the lens to distribute light asymmetrically between distant (65 percent) and near focus (35 percent), which the company says also results in improved intermediate vision.[3]

• ***RayOne trifocal.*** Rayner recently developed its own hydrophilic acrylic IOL for presbyopia called the RayOne trifocal, a lens with 16 rings in a 4.5-mm diffractive zone with a total optic diameter of 6.25 mm. The power range for this lens is zero to +30 D in increments of 0.5 D. The company says that the design of the RayOne trifocal is aimed at decreasing the incidence of visual disturbances and night vision problems. Rayner says it's also designed to be less dependent on pupil size or lighting conditions in order to improve vision and accommodation around the clock for near, intermediate and distance.

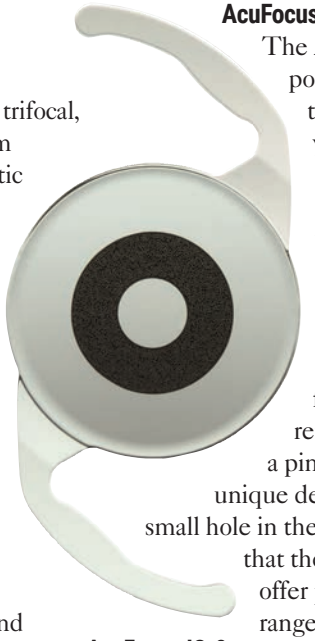
The company says the lens' patented diffractive step technology can transmit 89 percent of light to the retina with a 3-mm pupil. Roughly half the light is allocated for distance; the remaining half is divided between near and intermediate vision.

A study of 15 patients (30 eyes) comparing the performance of this lens to that of the FineVision POD F IOL (PhysIOL, Liège, Belgium) found that the RayOne trifocal demonstrated better refractive accuracy and milder issues with depth perception in patients than the latter, although other photic phenomena were not statistically different between groups.[4] Both IOLs were able to achieve positive visual outcomes in all patients. At three months postop, the study reported the mean monocular distance visual acuity to be 0.03 ± 0.11 (RayOne trifocal) and 0.04 ± 0.08 (FineVision POD F) logMAR (20/21 and 20/22, respectively); distance-corrected intermediate visual acuity, 0.05 ± 0.13 and 0.05 ± 0.10 logMAR (both around 20/22); and distance-corrected near visual acuity, 0.02 ± 0.12 and 0.03 ± 0.11 logMAR (both around 20/22).[4]

Clinical trials are still ongoing for this lens.

AcuFocus IC-8

The AcuFocus IC-8, possibly the closest in the pipeline to entering your practice, is a clear, aspheric monofocal lens that uses wavefront-filtering and small aperture technology to disrupt peripheral light rays and allow central focused light to hit the retina. In short, it creates a pinhole effect through its unique design of a ring with a small hole in the center. AcuFocus says that the IC-8 is designed to offer patients a continuous range of vision with fewer bothersome visual effects



AcuFocus IC-8

that typically accompany diffractive IOLs, such as problems with night vision and photic phenomena.

Just last month, on December 7th, the IC-8 received premarket approval from the FDA, which anticipates delivering official approval of the product upon completion of a series of pre-approval inspections across all manufacturing facilities.[5]

The 6-mm single-piece hydrophobic acrylic lens has a 2.23-mm-diameter opaque mask with a 1.36-mm central aperture. Using a unique injector system, insertion requires a 3.5-mm incision. In clinical trials investigating its ability to correct presbyopia, the company reports that, "Six months after implantation with a small aperture IOL in one eye, 99 percent, 95 percent and 79 percent of patients with presbyopia achieved 20/32 or better binocular uncorrected distance, intermediate and near visual acuity, respectively."[6]

"The advantage of the design of this lens is that it allows for non-focused or irregular light rays to be filtered out by the pinhole," says Mark H. Blecher, MD, co-director of the Cataract and Primary Eye Care Service at Wills Eye Hospital in Philadelphia and the chief medical editor of *Review*. "As a result, refractive error, including hyperopia, myopia and astigmatism, are minimized, and aberrant light from an irregular cornea is minimized. Ultimately, it improves the depth of focus of the eye and decreases the number of higher-order aberrations because the irregular light rays aren't allowed in. Depending upon your refractive target, it can give you good distance vision and it can give you depth of focus for intermediate vision."

Dr. Blecher says the desired target refraction may determine whether this lens will be a good choice for a given patient. "The effect is not powerful enough to provide a patient with full reading vision most of the time, but its success depends on what you're targeting the refraction to be," Dr. Blecher explains. "If you pick a myopic target, the patient will get more near vision, and the pinhole will still give them good distance vision." He notes that the recommended target for this lens is -0.75 D.

Y. Ralph Chu, MD, founder and medical director of Chu Vision Institute in Bloomington, Minnesota, is eager to be able to offer this new accommodative lens to various types of patients. "The IC-8 is exciting because it helps increase depth of focus through an aperture effect; there's really no other lens like that available right now in the market," says Dr. Chu. "Not only can it be used as a presbyopia-correcting IOL, but it could also be used potentially to help patients with irregular astigmatism or irregular corneas. I can picture a lot of patients with corneal disease—not just from previous refractive surgery, but from medical conditions like keratoconus, injuries to the eye where the pupil is damaged or irregular astigmatism caused by a corneal scar—possibly benefiting from the IC-8 and the improved quality of vision."

It's possible the IC-8 might be approved in 2022.

Perfect Lens

Now for something a little different in the pipeline: rather than a physical accommodative lens, this alternative method of presbyopia correction, the Perfect Lens (Perfect Lens, LLC), involves a femtosecond laser that can change the refractive power of a previously implanted lens. The innovative technology aims to offer a less-invasive solution to post-cataract surgery patients or those who received a presbyopia-correcting IOL previously and end up needing or desiring a different refractive power months or years down the line.

The Perfect Lens is currently only in the early phase of human trials outside the United States, but according to literature published so far, the results seem promising. The lens uses refractive index shape technology that involves adding water to designated areas of the pre-implanted lens, therefore changing its refractive characteristics, according to the company.[7] The company also says that laboratory studies show that "RIS technology can be used to change an existing IOL power of up to 3.6 D within 23 seconds while keeping a good modulation transfer function." The results also showed the technology is capable of switching a lens back and forth from multifocal to monofocal.[8]

"It's a pretty cool idea to have a truly customizable lens where, for the first time, it's been shown in the laboratory that you can take a monofocal lens and turn it into a multifocal lens and then turn it back into a monofocal lens without loss of quality of vision," says Dr. Chu. "In a way, it could be like an eraser for a surgeon. For example, a patient would be able to try multifocality, and if they can't tolerate the side effects at night or are unhappy with the outcome for whatever reason, then theoretically, according to laboratory results up to this stage, you could actually erase the multifocality with this technology and the patient could go back to monofocal lenses."

The advantages of reversibility and customization are the two major elements of Perfect Lens that set it apart from other presbyopic IOLs in the pipeline, notes Dr. Chu. "You can customize the prescription, astigmatism and presbyopia correction all with that same laser, but more importantly, you can reverse the correction, which is something that no other lens or IOL technology can do at this stage."

Juvene

The world's first modular fluid optic IOL, Juvene (LensGen, Irvine, California), is a premium lens for presbyopia in the pipeline that tries to help patients achieve true accommodation. The two-part lens is designed to mimic the effect of the natural crystalline lens, and it can be inserted through a 3-mm incision. It consists of a base lens that fills the capsular bag and a curvature-changing liquid silicone lens that fits into the

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base lens and allows for more seamless accommodation, which could offer patients a continuous dynamic range of vision from distance to near. Also, presbyopes bothered by visual dysphotopsias caused by IOLs with concentric rings may benefit from a non-ring, fluid-optic IOL such as the Juvene.

"The base lens keeps the capsular bag distended and hopefully clear, as well as provides a big chunk of the focusing ability that you need post-cataract," says Dr. Blecher. "Then, you have a second smaller lens component, the fluid lens, that you put in, which moves in the eye and changes shape to give you that accommodation on demand."

He brings up the point that when placing multi-piece IOLs, the rate of success in achieving targeted visual outcomes may decrease. "When you put these lenses in, you want the patient to have clear distance vision, so you have to hit your refractive target, and then the accommodative effect will provide the near. But, when you're working with a two-piece IOL like Juvene, the predictability of achieving that is a little less." Another downside of a multi-piece premium IOL, besides increasing the complexity of surgery, could be the likely higher cost.

Auspicious trial results were published by LensGen in 2019 from the company's Grail study, which involved 54 eyes implanted with the IOL by multiple surgeons (14 patients underwent bilateral implantation). In September 2019, Sumit Garg, MD, presented the following conclusions from the study based on one to six months of patient follow-up data: 100 percent of eyes achieved spectacle independence, 100 percent achieved 20/25 vision at distance and intermediate and 91 percent achieved 20/32 at near. The company also reported that no patients in the study experienced glare, halo or other dysphotopsia. Eric D. Donnenfeld, MD, presented the updated study's results on patient refractive outcomes at one year postop at the 2020 virtual American Academy of Ophthalmlology meeting. He reported that patients achieved a mean monocular CDVA, DCIVA and DCNVA of 20/20, 20/25+ and 20/32-2, respectively.[10]

The Juvene IOL received approval for an Investigational Device Exemption from the FDA at the end of November 2021, meaning the company may soon begin conducting human trials to study the safety and effectiveness of the lens.[11]

FluidVision

The FluidVision lens (Alcon/PowerVision) is another IOL that uses fluid inside the lens to provide what the company calls "true accommodation." The IOL is a hollow, acrylic single-piece lens that's placed in the capsular bag. The lens is filled with silicone fluid that moves in response to contraction or relaxation of the ciliary muscles. When the eye is in its natural accommodative state, a drop of fluid moves from the haptics to the center of the IOL, causing the IOL to slightly inflate and allow near vision. As the eye moves to its disaccommodative state, the lens deflates by squeezing the liquid back over to the haptics, yielding distance vision.

The FluidVision IOL has an optic diameter of 6 mm and a total diameter of 10 mm, making it larger than many other IOL models and therefore requires a wider incision. The company says the newest version of the lens, the FluidVision 20/20, can be implanted through a 3.5-mm wound using the PowerJect injector system; however, studies are under way investigating a model that will decrease the incision size required for insertion.

This lens is currently still in its investigational stage.

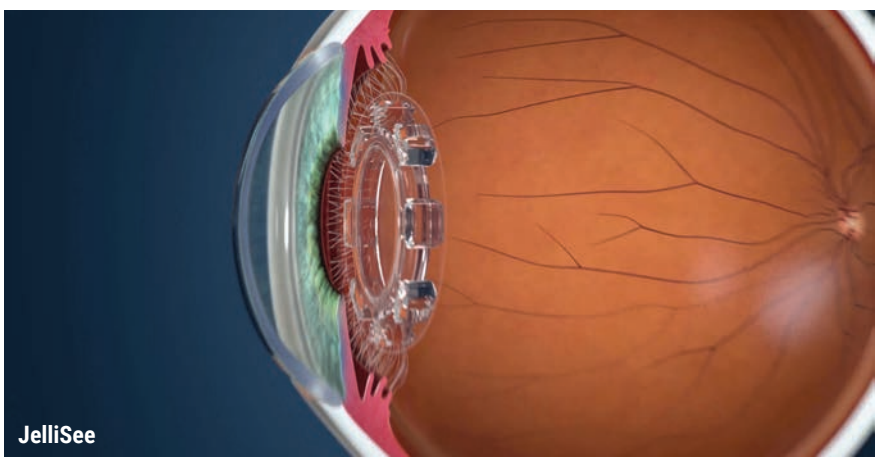
JelliSee

The newest addition to the growing list of presbyopic IOLs in the pipeline, the JelliSee (JelliSee Ophthalmics) accommodating IOL is a monofocal lens finishing up its preclinical stage that aims to provide presbyopes and astigmats with true accommodation.

The company says that, as the eye shifts its focus between near and distant targets, the flexible design of JelliSee permits it to react to natural forces of the ciliary muscle using technology similar to that used in the FluidVision and Juvene IOLs. As the muscle relaxes, the lens will flatten and increase in diameter in reaction to the force the zonules exert onto the lens capsule, enabling the focus to change from near to far.

One thing that sets this IOL apart from others, according to developers,

(Continued on p. 62)



Apellis is exploring the role of complement in Geographic Atrophy[1]

C3 is the linchpin of complement overactivation in GA.[2-7]

All three complement pathways converge at C3 and it drives multiple downstream effects — inflammation, opsonization, and formation of the membrane attack complex — all of which can ultimately lead to retinal cell death. Increased levels of complement activity have been found not just in the lesion itself, but also in the area just outside the lesion, known as the pre-lesion.[2-9]

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1. Katschke KJ Jr, et al. *Sci Rep*. 2018;8(1):13055. 2. Mastellos DC, et al. *Trends Immunol*. 2017;38(6):383-394. 3. Ricklin D, et al. *Immunol Rev*. 2016;274(1):33-58. 4. Heesterbeek TJ, et al. *Opthalmol Vis Sci*. 2020;61(3):18. 5. Seddon JM, et al. *Nat Genet*. 2013;45:1266-1370. 6. Yates JRW, et al. *N Engl J Med*. 2007;357(6):553-561. 7. Smailhodzic D, et al. *Ophthalmology*. 2012;119(2):339-346. 8. Boyer DS, et al. *Retina*. 2017;37:819-835. 9. Park DH, et al. *Front Immunol*. 2019;10:1007.

E-SURVEY: NEW IOLS BEGIN TO TAKE ROOT

Cataract surgeons who responded to our annual intraocular lens survey seem to be warming up to the latest additions to the premium-IOL armamentarium.

WALTER BETHKE
EDITOR IN CHIEF

It's always interesting to see how new intraocular lens technology fares as it tries to capture the interest of cataract surgeons. Physicians often take a watchful-waiting approach, ensuring that a new lens has the efficacy and safety profile they want before incorporating it into their everyday practice. This seems to be the case with the most recent additions to the premium IOL market, the Vivity (Alcon) and the Synergy (Johnson & Johnson Vision), though a fair number of respondents on this year's IOL survey have begun using them in patients already.

This is just one of the findings from this year's e-mail survey on IOL preferences. This time around, 22 percent of the 11,518 recipients on *Review*'s e-mail list opened the message, and 54 surgeons took the survey.

To read about your colleagues' impressions of the newcomers on the IOL scene, as well as other lens technologies, read on.

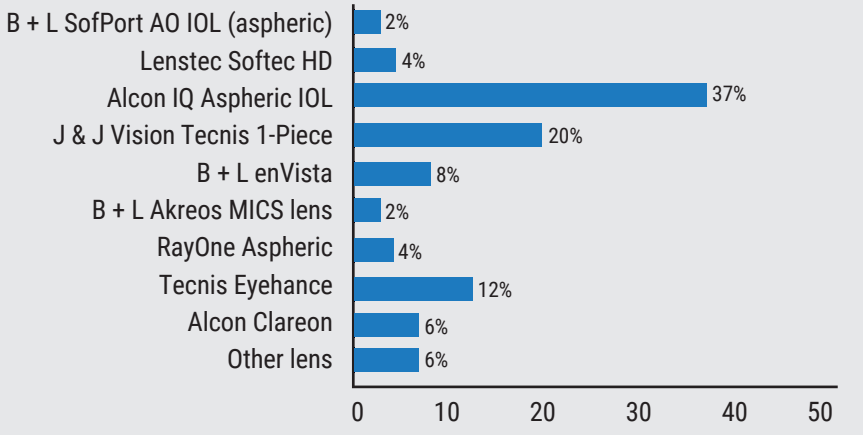
Premium Preferences

Surgeons who implant premium intraocular lenses are embracing technology such as trifocal IOLs, but are also warming up to the latest additions to the market.

The most popular premium lens option among the respondents (with some surgeons choosing more than one option) is the PanOptix Trifocal (non-toric), with 54 percent of the respondents saying they implant it (average number implanted per month: 8; average charge/eye: $2,705). Following the non-toric PanOptix was its toric counterpart, used by 46 percent of the physicians (average number implanted per month: 7; average charge/eye: $2,783).

A New York surgeon says he uses the PanOptix due to "less haloes and a crisper quality of vision." Another New York surgeon says he chooses the PanOptix because of "Excellent distance and near, with

Preferred Non-premium IOL for Most Cases



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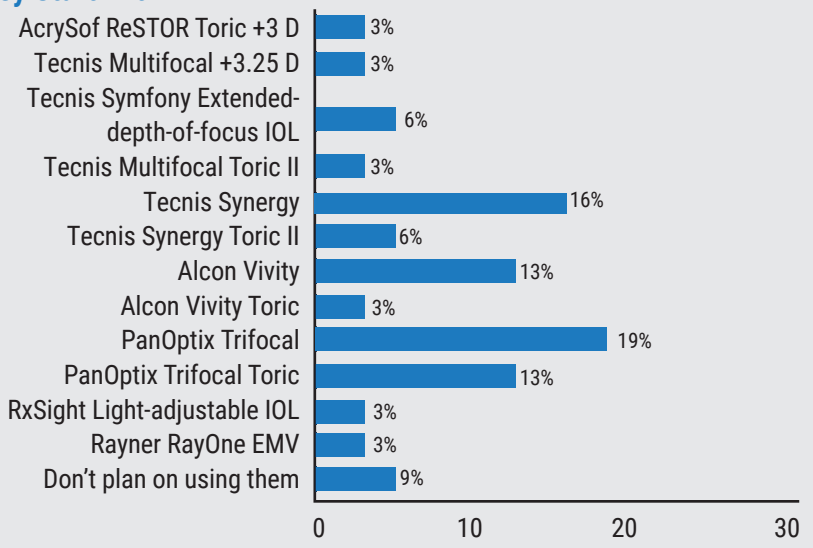
If Surgeons Start Using Presbyopic Lenses, Which Lens Will They Start With?



tolerable night distractions."

"[The PanOptix has] less dysphotopsia, more near vision, and is less dependent on ocular surface," says a surgeon from Cincinnati.

The next most popular group of premium lenses are the most recently approved ones, the Alcon Vivity and J&J Vision Tecnis Synergy lens families. The Vivity is a non-diffractive, extended-depth-of-focus IOL with a unique central optic zone. The Synergy has been described as a kind of mix between the Symfony and the Tecnis multifocal, since it combines elements of an EDOF lens with a diffractive multifocal to provide a range of vision.

Thirty-three percent of surgeons say they implant the non-toric Vivity (average number implanted per month: 7; average charge/eye: $2,524), and 24 percent implant the toric version (average number implanted per month: 6; average charge/eye: $2,911). Twenty-six percent of the surgeons on the survey implant the Tecnis Synergy (average number implanted per month: 9; average charge/eye: $2,656), and 22 percent implant the Tecnis Synergy Toric II (average number implanted per month: 6; average charge/eye: $2,599). Fifteen percent implant the original Symfony EDOF Toric II lens (average number implanted per month: 3; average charge/eye: $2,324).

A Los Angeles surgeon says, "Vivity is my favorite premium IOL because it gives an improved range of focus, largely without night driving glare problems."

New York's James Hu, MD, a Vivity user, likes the lens, but sees some room for improvement. "I get issues with late decentration; day one postop and one week postop, the IOL will be perfectly centered around the pupil, but at a month I've noticed the IOL will shift 0.5 mm (usually inferotemporal or superotemporal), despite following most of the pearls for IOL centration."

Oklahoma City ophthalmologist Deena Sylvester says, "I like that the Vivity doesn't have halos/glare, but I wish it could provide better 14- to 16-inch reading."

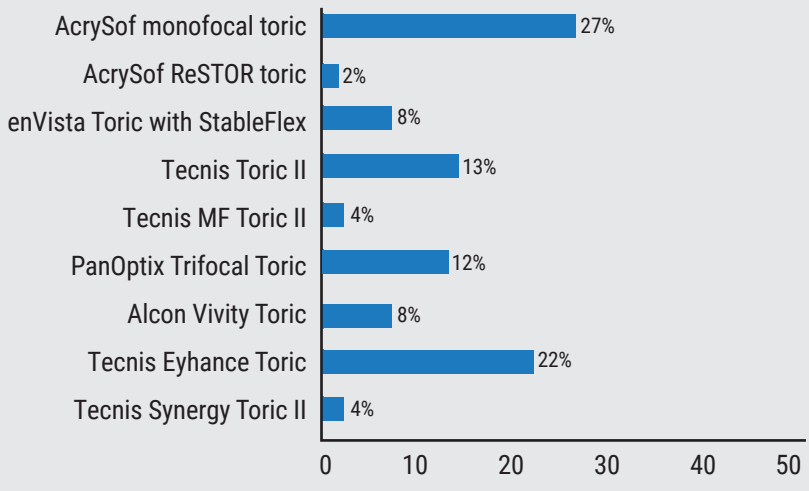
Colorado Springs surgeon Steve Dewey likes using the J&J Tecnis MF Toric II and the new Synergy. "I have to target appropriate refractive error, usually +0.25 D sphere. The J&J lenses give great contrast, amazing acuity and a fantastic range [of vision]."

Only 23 percent of the surgeons say they mix IOLs to give patients a greater depth of focus.

Dr. Dewey says he mixes-and-matches with the Symfony and the +3.25 Tecnis MF IOL, and includes the toric versions as necessary. "Mixing-and-matching is suitable for mild ocular pathologies (asymptomatic epiretinal membrane, presence of a few drusen, treatable dry eye)," he says, "knowing that we can't always predict the result of the surgery in light of minor pathologies. Otherwise, in a 'perfect' eye, Synergy bilaterally works great."

Dr. Sylvester says, "Very rarely do I mix-and-match. If the first

Preferred Toric IOL



IOL Attributes Surgeons Value (1= least important, 8=most important)

Attribute	Average score
Asphericity/neutral asphericity	5.33
Extended-depth-of-focus design	5.24
Toric design	5.02
Trifocality	4.49
Edge design to decrease PCO	4.38
Bifocal multifocality	4.07
Ability to adjust IOL power post-implantation	3.96
Blue-light blocking	3.83

eye with a Vivity isn't satisfactory enough for the patient at near, I'll consider PanOptix in the second eye. This has been good for the two patients I've done this in."

A Cincinnati surgeon says he doesn't mix-and-match because, "I'm nervous about patients noting subtle differences between their eyes."

Monofocal Mainstays

Surgeons also opined about the lenses they use for the bulk of their patients.

The Alcon IQ Aspheric was the single most popular choice, chosen by 37 percent of the respondents. The J&J Tecnis 1-piece was next, with 20 percent of the respondents preferring it. Twelve percent say they often use the new Tecnis Eyhance, and 8 percent prefer the B+L enVista.

A surgeon from Georgia who uses the Alcon lens says, "I like the gentle opening in the bag. I dislike the 6-mm optic (would prefer 7-mm), the lack of a square edge for delaying PCO, and that the haptics don't open enough or have enough spring for unassisted centering."

Dr. Dewey uses the Tecnis 1-piece. "It yields good acuity, amazing contrast and is relatively forgiving with good acuity over a small range of refractive errors," he says. A physician from New Orleans also uses the J&J lenses, and sees strengths and weaknesses in each. "I like the full range of vision with the Synergy," he says. "I don't like the nighttime glare. It's the opposite with the Eyhance: It gives marginal near vision, but there are no complaints with night driving. I use more Eyhance than Synergy."

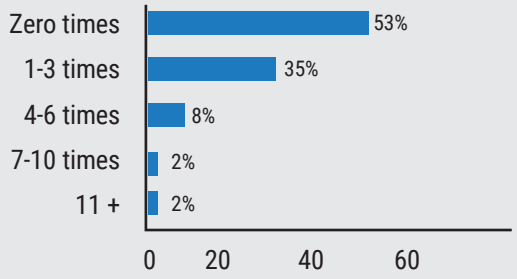
A Kansas surgeon who prefers the enVista says he does so because "There are no glistenings, and it has a durable surface that won't scratch."

Toric IOLs

For tackling patients' astigmatism with an IOL, the most popular option on the survey was the AcrySof monofocal toric (27 percent), followed by the Tecnis Eyhance toric (22 percent). Fourteen percent say they prefer the Tecnis Toric II and 12 percent like the PanOptix trifocal toric.

Robert Mobley, MD, of Clinton Township, Michigan, says that he likes the AcrySof monofocal toric for its "good stability and centration." Colorado's Dr. Dewey uses the new Eyhance. "I appreciate the enhanced range of the Eyhance, and I appreciate how the frosted haptics reduce post-implantation rotation," he says.

How Often Surgeons Suture an IOL in a Year



Phakic Lenses

Only a fifth of the respondents say they implant phakic IOLs, with the majority of them (91 percent) preferring to use the Visian toric or non-toric. The rest say they implant the Artiflex/Veriflex.

A Cincinnati surgeon who uses the Visian says, "It's easy to insert, has great optics, and the material is easy to work with. Loading is challenging and looking forward to not having to create PIs [with the upcoming Visian EVO]. A surgeon from Los Angeles agrees, saying, "It's a much better option than LVC, especially in moderate to super-high myopes if they're sufficient candidates." St. Louis' Krishnarao Rednam says the Visian "gives good outcomes."

Suture Situations

The respondents also discussed suturing IOLs. Fifty-three percent say they usually don't have to suture an IOL in any given year, and 35 percent say they find themselves suturing a lens one to three times in that span.

The main reasons given for suturing lenses:

- loss of zonular support due to pseudoexfoliation;
- late bag and lens dislocation;
- missing zonules; and
- immunosuppressed patients who are poor healers.

In the end, surgeons seem content with their lens options, but there's a sense that the ideal premium lens has yet to arrive. Says Minneapolis surgeon Jesse Dovich, MD, "We need a fully accommodative IOL." ◀

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MANAGING CME AFTER CATARACT SURGERY

Cystoid macular edema following cataract surgery is rare, but when it does occur, knowing what to do next is key.

CHRISTOPHER KENT
SENIOR EDITOR

Pseudophakic cystoid macular edema can be a confounding complication of even the most carefully planned cataract procedure. Although pseudophakic CME doesn't occur a lot postop, this means it's not studied a lot, so surgeons often must go on their own clinical acumen when treating it.

In this article, experts explain how they work up and treat cases of pseudophakic CME, from the mild to the recalcitrant.

Risk Factors

The American Academy of Ophthalmology's *Preferred Practice Patterns* defines this condition as retinal thickening of the macula due to a disruption of the blood-retinal barrier, causing leakage from the perifoveal retinal capillaries. The leakage leads to fluid accumulation in the retina, distorting the architecture of the photoreceptors and potentially causing central vision loss.

How big a problem is this among cataract surgery patients? Phoebe Lin, MD, PhD, a retina and uveitis specialist and an associate professor at Casey Eye Institute, at Oregon Health & Science University in Portland, notes that some studies have found that about 2.4 percent of small-incision phaco patients develop pseudophakic CME. "Of course, people with pre-existing diabetic retinopathy can get diabetic macular edema," she says. "However, even without a risk factor like that, it still seems to occur about 2 percent of the time. Why it occurs when you don't have diabetic retinopathy or a prior history of inflammation is a little unclear."

Sruthi R. Arepalli, MD, a uveitis and vitreoretinal surgeon at Tennessee Retina in Nashville, points out that it's difficult to say exactly how many cataract surgery patients develop postop CME. "It depends on how you define it," she explains. "For example, you can define it clinically. That means looking at it with a slit lamp; I can see the edema, and it's causing some sort of visual decline. But you can also find cysts on OCT or fluorescein angiogram; those may not be visually significant, and they may not be things that we need to treat. As a result, risk calculations based on OCT and fluorescein angiograms are higher than numbers based on clinical exam."

Naturally, surgeons would like to know which patients are more likely to develop CME post-cataract surgery. "Risk factors for CME after cataract surgery include diabetic retinopathy; an epiretinal membrane; a history of uveitis; and/or a prior history of macular edema related to something like a retinal vein occlusion," notes Chirag P. Shah, MD, MPH, a vitreoretinal surgeon at Ophthalmic Consultants of Boston, an assistant professor at Tufts University School of Medicine and a lecturer at Harvard Medical School.

Dr. Arepalli lists a number of things that lead her to warn patients that postop CME is a possibility. "First, patients with diabetes are at higher risk, even if they don't have retinopathy, because their vessels are leakier," she says. "Second, if a patient has a very small pupil or posterior synechiae, I know there will be pupillary manipulation during the cataract surgery; that can release

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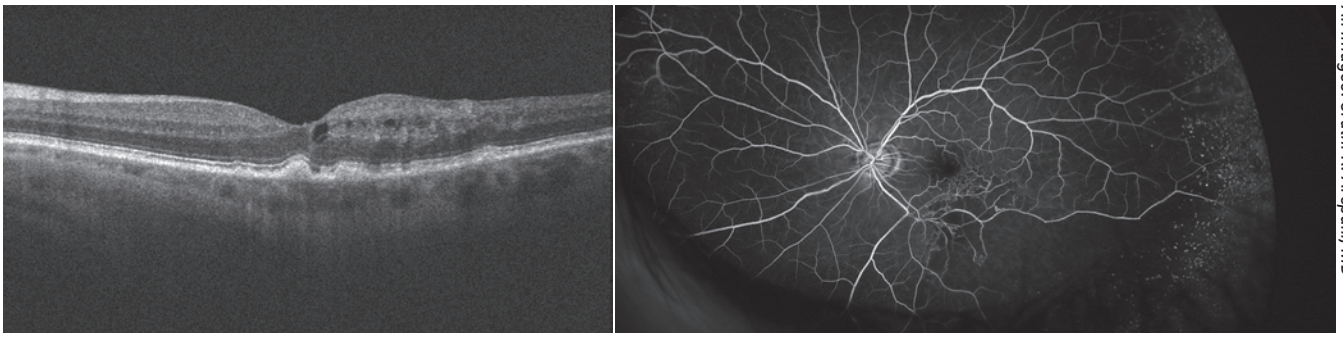
Drs. Lin, Shah and **Arepalli** report no relevant financial ties to any product mentioned in the article.



All images: Sruthi R. Arepalli, MD

A 73-year-old male previously followed for dry macular degeneration was sent for evaluation for supposed pseudophakic CME versus conversion to neovascular macular degeneration following cataract surgery. Fundus examination revealed drusen in the macula and edema, but no signs of choroidal neovascular membrane on optical coherence tomography or fundus examination. Inferotemporally, the vessels appeared sclerotic and a fluorescein angiogram was useful in diagnosing a branch retinal artery occlusion with macular edema which was treated with anti-VEGF therapy.

a cascade of cytokines, resulting in CME. Third, a person with an epiretinal membrane is more at risk. Fourth, if I'm following a patient for retinal vein occlusion, even if they haven't had macular edema in the past, their risk is higher; like patients with diabetes, their vessels are leakier than normal. Also, if the patient has a history of uveitis, their eye already tends to be more inflamed, making them more susceptible.

"Other things that can increase the risk of postop CME include differences in eye architecture," she continues. "If the posterior capsule ruptures during the surgery for any reason and the vitreous is unstable—it comes forward or even gets stuck in the cataract wound—that can lead to CME. The risk also increases if there's an iris-sutured lens, or an anterior chamber lens that's causing some chafing and moving around, or the lens placed in the bag becomes dislocated and falls back.

"I always tell patients, as well as our residents and fellows, that CME following cataract surgery can occur in both complicated and uncomplicated surgeries," she says. "It involves the release of prostaglandins and inflammatory markers, causing an influx of fluid via leakage from the perifoveal capillaries and other sources. It can happen even when the surgery goes flawlessly, but it happens more often in patients who require a lot of manipulation inside the eye or have some sort of a surgical complication.

"Also," she adds, "some reports have suggested that patients who are on prostaglandins such as latanoprost may be predisposed to CME development, although this is a subject of debate."

Dr. Lin points out that most cataract patients do get some limited degree of postop inflammation. "Unfortunately, there's no test you can do ahead of time to predict who's going to get pseudophakic CME," she says. "Luckily, it's not very common, and typically it's self-limiting. However, that means it's not something anyone would perform a huge study on to try to identify the risk factors. Pseudophakic CME can present with scant vitreous and/or anterior chamber cells and optic disc leakage."

Initial Treatment

"It's not uncommon to develop minimal macular thickening after cataract surgery," Dr. Shah points out. "CME will usually manifest within a few months after the operation. Often, it's mild and not visually significant, causing no symptoms. It may be apparent on OCT or angiography, but not to the patient. Typically, I only treat if the patient is symptomatic from CME, or if it's significant on OCT. If it's not affecting or harming the vision, it's reasonable to monitor it."

Dr. Shah believes any treatment should be based on the apparent cause of the macular edema. "I employ a stepwise approach," he explains. "First, I do a comprehensive exam to determine if there are any other underlying risk factors for the macular edema. If it's just Irvine-Gass pseudophakic macular edema, it will often respond well to topical anti-inflammatory drops; once the macula is dry, I gradually taper the patient off the drops. If the cataract surgery exacerbated a patient's diabetic macular edema, one can start treatment with anti-inflammatory drops. However, one might need to treat the diabetic macular edema. The same is true for other underlying causes such as retinal vein occlusion or macular puckering."

Dr. Lin says patients referred to her typically have developed unexpected residual CME about one month after cataract surgery. "In most cases these patients are already on a topical steroid like prednisolone and an NSAID like ketorolac or diclofenac," she says. "A steroid with an NSAID is a pretty reasonable first-line treatment for pseudophakic CME; it's routinely employed for diabetic patients post-phaco. Usually, patients are tapered off by one month, although if the referring physician still sees CME, they might prolong the use of those drops.

"When I see the patient, treatment is typically a step-wise proto-

SHOULD YOU TREAT PREOPERATIVELY?

Sruthi R. Arepalli, MD, a uveitis and vitreoretinal surgeon at Tennessee Retina in Nashville, says she believes deciding whether to start the patient on drops prior to cataract surgery is largely a question of surgeon comfort. "I've seen some cataract surgeons who start drops before the surgery to try to limit inflammation, and some who don't," she notes. "I think either choice is appropriate. Presumably, the choice is based on what they've seen in their patient population.

"If you're seeing a patient who has a risk factor for postop CME such as diabetes, an epiretinal membrane, a previous retinal vein occlusion or something leading you to expect a complicated surgery or postop course, then placing the patient on a topical NSAID and Pred Forte four times a day in the week or so preceding surgery is totally reasonable," she says. "This regimen is usually pretty inexpensive and well-tolerated, with a very low side-effect profile.

"Of course," she adds, "if the patient is uveitic, it makes sense to defer to their uveitis provider to make sure the eye is totally quiet before you do the cataract surgery. You don't want to be entering a hot eye."

—CK

col, but individualized," she adds. "If the patient isn't already on prednisolone and ketorolac, I usually try that for about a month."

"Most surgeons I've encountered feel very comfortable starting with a topical NSAID—generally ketorolac, though there are other options as well—and Pred Forte, four times a day," says Dr. Arepalli. "Generally, they follow the patient for a month to see if it starts to get better. If it doesn't, they may send the patient to a specialist.

"If I see a patient with a little bit of pseudophakic CME, and their vision is generally 20/30 or 20/20, I'll first do a fluorescein angiogram and OCT to make sure I'm really treating pseudophakic CME," she continues. "If it really is CME, but the patient has good vision and only trace fluid, we can treat or we can watch for a while—whichever the patient prefers. I usually give them about a month to show that they're improving before moving ahead with treatment. If the patient gets better over time, I usually keep them on a four-times-a-day regimen until their fluid resolves. Then I'll start to taper off the drops.

"I don't advise tapering before the fluid is completely gone," she adds. "I've tried that, and in some patients the fluid starts to come back."

Why do many surgeons opt for using steroids and NSAIDs together? "NSAIDs are anti-inflammatory, but they're not very potent medications, in terms of treating cells or macular edema," says Dr. Lin. "However, they're not completely inactive, and they don't cause elevated eye pressure. They can treat mild CME, and they have nice adjunctive properties when used along with topical steroids; they can sometimes reduce the amount of steroid you use. Some patients are steroid responders, so adding NSAIDs can be a benefit to the patient, lowering their steroid burden and thus reducing steroid-related side effects."

"I use both Pred Forte and Acular because published studies have looked at steroid drops alone, vs. topical NSAIDs alone, vs. both used together," notes Dr. Arepalli. "Although there are no randomized controlled trials looking at this question, it's clear that the greatest benefit comes when both are used together. The steroid drops also let us see if the patient has a steroid response, in case we consider more invasive steroids in the future."

Stepping It Up a Notch

"If a patient referred to me is already on a topical steroid and an NSAID and still has CME, that tells me the problem is more severe than what those two drops can handle," says Dr. Lin. "My next step would be to put them on a more potent steroid drop. There's one called difluprednate, which is more highly penetrating, and it can also be used at a lower frequency than prednisolone. So, I'll typically escalate to that first and give the CME about one month to improve. We don't put patients on that drop initially because it has a higher rate of elevated IOP as a side effect."

Dr. Lin says that if the severity of the CME is beyond what she thinks can be treated by difluprednate alone, then she might offer a posterior sub-Tenon's steroid injection or an intravitreal steroid injection. "I also do a very thorough bilateral exam for other signs of inflammation," she notes.

"For instance," she continues, "bilateral inflammation would suggest that the patient might have an underlying uveitic process that wasn't recognized previously. Or, I might see other signs such as chorio-retinal scarring or other signs of prior inflammation. In that situation, I'll take a step back and start working up the patient for causes of uveitis. However, if it's run-of-the-mill pseudophakic CME, and the patient doesn't have any other signs of infectious uveitis or bilateral, systemic endogenous uveitis, then I'll go up the stepladder of steroid treatment."

Dr. Shah says that if topical treatment doesn't resolve the CME, he'll also consider a sub-Tenon's Kenalog injection. "This is usually unnecessary," he says. "However, if it's needed it will improve the CME in most cases, and it can be repeated. In the small portion of patients for whom a sub-Tenon's Kenalog injection isn't helpful, I'd consider an intravitreal steroid injection next."

Dr. Arepalli says if the topical drops are well-tolerated but produce insufficient response, then she'll discuss other options with the pa-

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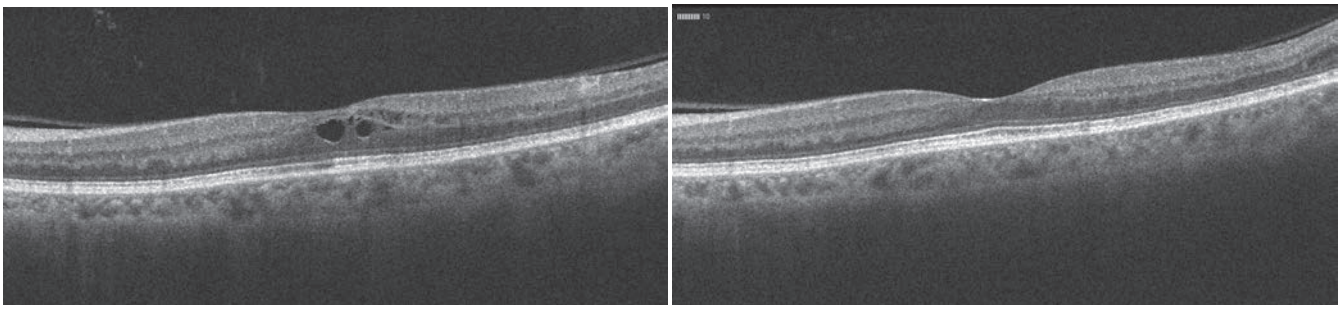


A 68-year-old female presented one month after cataract surgery in the left eye (left) with vision decreased to 20/40 and a small amount of cystoid macular edema. She was treated with a combination of Pred Forte and a topical NSAID, with resolution of the fluid at six weeks (right).

tient. "Those options would include periocular corticosteroids," she says. "Those have been shown to be effective in cases of refractory CME.

"Intravitreal triamcinolone has also been used and shown to be effective," she continues. "The downside of using intravitreal triamcinolone is that it has a short therapeutic window, so you have to keep giving it to patients. And once you start going down the intravitreal route, you're talking about a more potent corticosteroid with a greater likelihood of triggering an IOP increase. If the patient still isn't responding, or they have refractory CME that keeps coming back, then you can start discussing long-lasting drug depots, like Ozurdex or Yutiq, which have been approved for posterior uveitis."

"I do think if it gets into the arena of the patient needing increasing dosages or injections, that's best left to a retinal or uveitis specialist," she adds. "They're very experienced at monitoring the retina and looking for clues about other reasons this might be happening."

Treating With Anti-VEGF

One option that may be appropriate to use with some patients is anti-VEGF injections. "Some patients have presumed postop macular edema, but without the other signs of intraocular inflammation," notes Dr. Lin. "For instance, they don't have anterior chamber cell or vitreous cell along with the macular edema; they look quiet. Those are good candidates for anti-VEGF.

"I've also used anti-VEGF for patients who are very sensitive to steroid-induced elevated eye pressure," she continues. "Or, I get a referral where other things have been already tried without success. The patient may already have had a spike in eye pressure while using the regular postop drops. In that case, I may go straight to anti-VEGF treatment."

"I'd consider anti-VEGF injections for patients with macular edema as a result of diabetic retinopathy or retinal vein occlusion," notes Dr. Shah. "Furthermore, intravitreal steroids might be necessary."

In this situation, Dr. Lin says it makes sense to treat with close observation. "You usually wouldn't inject more than once a month, so you'd be bringing the patient back monthly to see how they respond and whether the edema recurs," she says. "This is not a chronic, progressive disease like macular degeneration; it's typically self-limited to a year at most. If it lasts more than a year, it's usually something else completely.

"For that reason," she explains, "the treatment wouldn't follow a macular degeneration protocol. You wouldn't need to have a three-month start-up phase and then go to treat-and-extend. In any case, by the time you're trying anti-VEGF with one of these patients, the problem has existed for several months, so they're near the end of the postop inflammation—assuming the problem really is pseudophakic CME."

Dr. Arepalli says she reserves anti-VEGF injections for use as a last resort. "I save anti-VEGF injections for a more selective group of patients—those I think might have more of a VEGF-driven problem," she explains. "That would include diabetic patients and those who've had retinal vein occlusions or macular degeneration—something that makes me think there's a cascade of inflammation, and that VEGF would be a good target."

The other question regarding anti-VEGF injections is: Who should perform the injections? Dr. Shah says he believes the decision about whether to perform intravitreal injections oneself or refer to a retina specialist is mostly a question of availability. "Where I practice, in Boston, cataract surgeons typically don't do intravitreal injections," he notes. "They usually refer to retinal specialists, who are readily available. On the other hand, in some parts of the country, comprehensive ophthalmologists do their own anti-VEGF injections because the nearest retinal specialist might be hours away. I think it depends on the region in which one practices."

If anti-VEGF injections are given, Dr. Arepalli favors having them performed by a surgeon who's comfortable administering them. "Typically, that means someone who's been

trained to do them, and trained to deal with their possible complications," she says. "That's why I wouldn't want to do glaucoma surgery; I don't do it every day. If there's no one available besides the cataract surgeon, and the surgeon feels comfortable doing it, and does injections routinely, I think that's reasonable. But I'd always prefer to see injections done by someone who does them regularly."

Systemic Treatment

Dr. Lin points out that most cases resolve within six months or a year. "That's why I go with local therapy rather than systemic therapy," she explains. "Some cases are more prolonged, but at that point you're thinking the patient must have some kind of underlying inflammatory process.

"Sometimes it takes additional testing to tease out the fact that the patient has an underlying inflammatory condition," she notes. "There have been times when we thought a patient had pseudophakic CME, but we weren't sure because the patient had such a complex surgical history. "Usually within two visits I'd do a fluorescein angiogram and discover that the patient had bilateral asymmetric inflammation from an underlying uveitic condition such as sarcoidosis; it just wasn't detected by run-of-the-mill testing and examination. It happened to worsen postoperatively."

"If the patient has uveitis," says Dr. Shah, "you can start with topical anti-inflammatory drops, but the patient might need more potent anti-inflammatory treatment to resolve the edema. This could include periocular or intravitreal steroids, or systemic immune suppression. It depends on the overall picture."

Dr. Lin adds she never uses a systemic immunosuppression treatment for typical pseudophakic CME. "I only go that route if the patient has other signs of inflammation," she explains. "Those are the patients who were misdiagnosed as having pseudophakic CME."

Strategies for Success

Surgeons offer these tips for ensuring the best possible outcome:

• ***If possible, do a preop dilated exam of both eyes.*** "Sometimes the patient has a dense cataract, making this impossible," Dr. Lin notes. "However, a bilateral dilated exam can identify an indolent, undetected factor such as diabetic retinopathy or an underlying uveitic process, which you obviously want to know before proceeding with the surgery."

• ***Consider adding the possibility of CME to your consent.*** "As surgeons, we typically focus on the most consequential possible complications when getting patient consent," notes Dr. Lin. "We may not consent for some things like inadvertent ptosis after surgery, or pseudophakic CME, because they're usually not as visually consequential as something like endophthalmitis. However, it's good to let the patient know that such things can occur. You can explain that there's a possibility of CME, even if the surgery goes perfectly and everything looks great ahead of time. It's an unpredictable potential complication."

Dr. Arepalli says she believes it's reasonable that the possibility of postop CME be included in the consent discussion. "It's a tough call because providers have to walk a line," she admits. "You want to give the patient all the information you can, but you don't want to overwhelm them, and there's no way to talk about every single possible complication. However, I think it's very reasonable to mention this when a patient has high-risk factors."

• ***Set realistic patient expectations.*** "If your patient has a preexisting condition that could trigger postop CME, I think it's appro-

TREATING GLAUCOMA WITH OSD: YOUR OPTIONS

These two conditions can be challenging to treat when they occur together. Experts offer their advice.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

Encountering dry-eye signs and symptoms in glaucoma patients is fairly common. Chronic use of IOP-lowering medications that contain preservatives is often the culprit, coupled with the fact that both diseases tend to affect an older population.

"It puts patients in a difficult position because they rely on these medications to control their glaucoma, but those same medications may be causing or exacerbating their ocular surface disease," says Sarwat Salim, MD, FACS, a professor of ophthalmology and director of the Glaucoma Service at the New England Eye Center at Tufts University School of Medicine in Boston. "Considering the effect OSD and glaucoma have on quality of life, it's important to take steps to reduce preservative exposure."

In this article, experts discuss some of the medical, procedural and surgical options for managing glaucoma-related OSD.

OSD Testing

Devising a management strategy starts with recognizing that your patient has OSD. Dr. Salim says this step is critical but often challenging because the signs and symptoms of OSD don't always align. "An asymptomatic patient might have severe surface staining and MGD, and a symptomatic patient might have only minimal surface staining," she says. "The level of comfort or discomfort patients feel isn't always a reliable means of assessing OSD. Incorporating OSD testing, such as TBUT, surface staining and Schirmer's test in your management of glaucoma patients can help you identify who needs treatment and which dry-eye mechanism is behind it.

"MMP-9 and osmolarity testing are also particularly useful," she continues. "One can use InflammaDry (Quidel) to evaluate MMP-9 levels in the tear film. It's common for glaucoma patients on preserved medications to exhibit elevated MMP-9 levels; this indicates an inflammatory etiology. In such cases, consider reducing the number of medications with preservatives or starting anti-inflammatory treatment."

To assess a patient's level of evaporative dry eye, she performs osmolarity testing. "Osmolarity is a balance of evaporation, drainage and tear production," she says. "It can be tested with a handheld osmometer (TearLab) to assess the level of evaporative dry eye. When patients have hyperosmolarity, their tears evaporate too quickly. We often see this in patients on topical glaucoma medications." The TearLab osmolarity system defines abnormal osmolarity as >300 mOsm/L or when the inter-eye difference is >8 mOsm/L.

"Additionally, ocular surface interferometry and infrared meibography (LipiView, Johnson & Johnson Vision) can help you assess, respectively, the tear film

This article has no commercial sponsorship.

Dr. Salim is a consultant and speaker for Aerie Pharmaceuticals. **Dr. Rapuano** is a consultant for Bio-Tissue, Dompé, Glaukos, Kala, Oyster Point, Sun Ophthalmics, Tarsus and TearLab. **Dr. Farid** is a consultant for Allergan, Bausch + Lomb, BioTissue, CorneaGen, Dompé, Tarsus, Orasis, Johnson & Johnson Vision, KALA, Novartis, Sun Pharmaceutical and Zeiss. **Dr. Bournias** has no related financial disclosures.

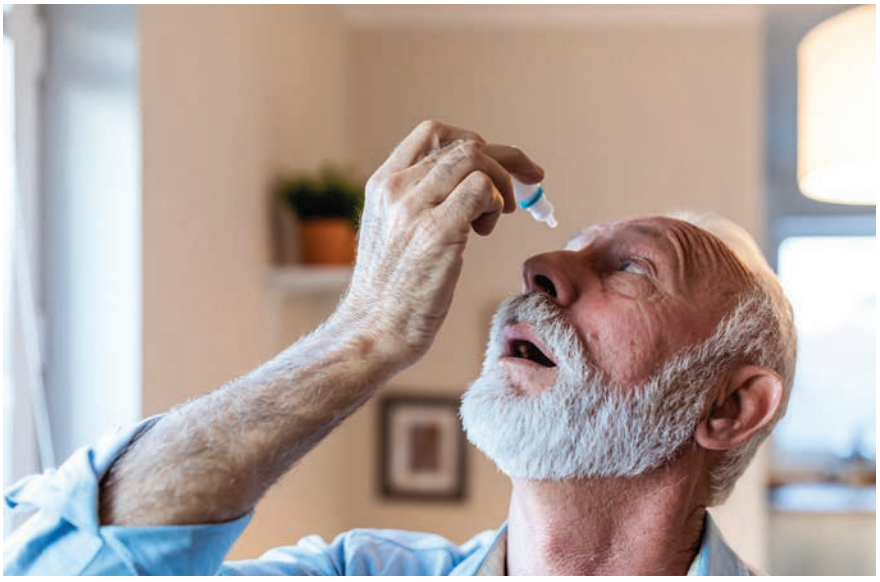
lipid layer and meibomian gland structure," she notes. "These data will help you determine the type of treatment your patient needs." Dr. Salim recommends performing dry-eye tests at baseline and at regular intervals to monitor the impact of treatment interventions.

Reducing Preservatives

Preservatives play an important antimicrobial role in multidose ophthalmic medications, but they may also cause irritation, redness and overall discomfort, particularly with concurrent MGD or blepharitis. Benzalkonium chloride, the most widely used preservative, is toxic to the cornea, yet it also improves the effectiveness of some medications by disrupting the junctions of the epithelium to facilitate drug penetration into the eye, according to Thomas E. Bournias, MD, a glaucoma specialist, the director of the Northwestern Ophthalmic Institute and an assistant professor of clinical ophthalmology at Northwestern University School of Medicine. "It has an additive effect on the corneal surface, so the higher the concentration and/or the more BAK-containing medications a patient is on, the greater the effect," he says.

Dr. Salim says that expanding the number of preservative-free glaucoma medication options and making them affordable and accessible would help to reduce the burden of OSD in glaucoma. "We know that switching to preservative-free formulations leads to improvement in dry eye," she says. "Currently, however, it's not always possible to switch a patient's glaucoma drops to preservative-free formulas. Availability is one issue, and cost is another."

"If you can't avoid BAK, using a lower amount can help," says Dr. Bournias. "Some patients can tolerate drops with lower concentrations of BAK such as Xalatan (BAK 0.02%, Pfizer) or Combigan (BAK 0.005%, Alcon)." *(For more BAK alternatives, see the table on page 46.)* Dr. Bournias adds that he's also used Xelpros (Sun Pharma), a non-BAK latanoprost and Catioprost (Novagali), an unpreserved latanoprost-cationic emulsion, for OSD patients.



Chronic use of topical, preservative-containing glaucoma medications can cause or exacerbate ocular surface disease. The literature also suggests an association between the number of drops a patient takes and their compliance with medication: The more complex the regimen, the lower the compliance, which may result in glaucoma progression. Fixed-dose combination drops may help address this, while limiting preservative exposure.

An additional benefit of preservative-free medication is the single-dose vials they come in, experts say. "Many patients enjoy the convenience of having a vial or two of drops for the day," Dr. Bournias says. "It's difficult for patients to refill their multidose bottles if they run out too soon (e.g., in the event they squeeze out too much) but the individual vials tend to last them the whole month."

"One other option to decrease preservative exposure is to convert your patient's glaucoma medications to fixed-dose combination products," says Dr. Salim. "Compounding pharmacies have affordable fixed-dose combination formulations of preservative-free glaucoma medications such as dorzolamide/timolol and brimonidine/timolol."

She says that combination products have the added benefit of greater simplicity for the patient, leading to increased compliance with fewer drops to instill. "Combination drops also help to avoid the washout effect, which often happens when patients quickly instill multiple medications, one after the other. However, you aren't able alter the concentrations of the individual medications or the time of day they're administered when the drops are combined."

Christopher J. Rapuano, MD, chief of the Wills Eye Cornea Service and a professor of ophthalmology at Sidney Kimmel Medical College of Thomas Jefferson University in Philadelphia, notes that there are a number of systemic medications that can cause dry eye, so it's important to ask your patients what other medications they're taking. "Antihistamines such as Benadryl dry out the sinuses, which is great for some sinus conditions, but it also dries out the eyes," he explains. "Certain cardiac

medications such as beta blockers can also cause dryness, and some diuretics like Lasix (furosemide) may dry out the eyes. We're not telling patients to stop their cardiac or COPD medications, but we may contact their cardiologist or internist to let them know that the medication is causing dry eye and ask whether there are any other equally efficacious medications that the patient can try that won't cause dry eye as a side effect."

Treating the OSD

In addition to withdrawing preservatives or other medications that may cause dry eye, clinicians turn to traditional OSD management approaches to alleviate glaucoma patients' eye irritation. Experts say clinicians should consider not only the mechanisms and degree of OSD severity, but the individual patients' abilities regarding treatment adherence.

Dr. Bournias says that "If patients are already taking glaucoma drops, it can be difficult for them to add yet more drops to treat their dry eye. Instilling the drops may be physically difficult, and adding more drops to treat OSD may decrease their compliance due to the complexity of the regimen and the irritation caused by the drops themselves if they contain preservatives."

He says that if a patient hasn't been treated for glaucoma yet and the glaucoma is mild or recent onset, he may treat the ocular surface before initiating glaucoma treatment. "We would, of course, initiate the treatment right away if the pressures were really high or the glaucoma were more advanced," he notes.

Here are some options for treating glaucoma-related OSD:

• ***Artificial tears.*** Dr. Bournias says he likes to start simple. "I begin with lubricating tears and give patients samples of what's available in the office," he says. "I often step it up to preservative-free artificial tears that come in vials."

Dr. Rapuano says, "We often recommend that our G-OSD patients instill an artificial tear drop five minutes before instilling glaucoma medications so that their eye is less susceptible to irritation. They can continue to use the artificial tears five minutes later to bathe the eye. Additionally, if the OSD is severe, it can affect a glaucoma patient's perimetry. We usually overcome this by giving the patient some drops before and during the visual field test."

> **Don't be afraid to get the inflammation under control at the outset.**
>
> ***—Thomas E. Bournias, MD***

• ***Anti-inflammatory medications.*** "When co-managing glaucoma patients, we'll often switch them from tears with preservatives to tears without preservatives, or prescribe anti-inflammatory medications such as Restasis (cyclosporine 0.05%, Allergan), Cequa (cyclosporine 0.09%, Sun Pharmaceuticals) or Xiidra (lifitegrast 5%, Novartis)," notes Dr. Rapuano.

"These medications help patients produce more tears by controlling inflammation," explains Dr. Bournias. "I tell patients that the prescription medications can take time to work, and that they may still need to use artificial tears—hopefully less frequently or not at all. Patients may have a better response to artificial tears once they're on the prescription medication. Xiidra and Restasis [and Cequa] don't have BAK, of course, so while this would add a drop to the regimen, it wouldn't cause further inflammation."

• ***Punctal occlusion.*** "Punctal plugs are easy, safe and tend to be covered by insurance," says Dr. Bournias. "However, if the patient has a significant amount of OSD with MGD or blepharitis, I generally won't use punctal plugs until the ocular surface is cleaned up, because using plugs early on will block the drainage of the tear film. That inflamed tear film has oil buildup, mucus and other inflammatory debris, and we don't want that material staying on the eye. The ocular surface should be clean before occluding the punctum with a plug."

• ***Steroids and antibiotics for lid inflammation.*** As long as he's able to closely monitor the glaucoma patient, Dr. Bournias says he feels comfortable using a mild steroid for a short period of time (one to three weeks) such as Lotemax SM (loteprednol etabonate 0.38%, Bausch+Lomb), Eysuvis (loteprednol etabonate 0.25%, Kala Pharmaceuticals) or fluorometholone. "Don't be afraid to get the inflammation under control at the outset," he says.

Antibiotic drops such as fluoroquinolone and ofloxacin are also useful for clearing up the lids if there's bacterial buildup, Dr. Bournias adds. "Azasite (azithromycin 1%, Akorn) is quite nice because it's thick," he says. "I prefer the thicker drops because they tend to stay on the lid. Ointments such as azithromycin or tobramycin/dexamethasone, if you want a steroid effect, can be applied at night since they blur the vision."

• ***Lid hygiene.*** "If steroids or antibiotics don't work sufficiently or the patient needs further therapy, we tend to turn to hygiene treatment," he continues. "We instruct the patient to clean their lids with a Q-tip, warm water and baby shampoo, or Ocusoft Lid Scrub or another type of lid scrub. Sometimes we recommend a spray such as Avenova (hypochlorous acid 0.01%)

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TABLE 1. A SAMPLE OF GLAUCOMA MEDICATIONS AND THEIR PRESERVATIVES

Medication	Active Ingredient	Preservative
Xalatan	latanoprost 0.005%	BAK 0.02%
Lumigan	bimatoprost 0.01%	BAK 0.02%
Combigan	brimonidine/timolol 0.2%/0.5%	BAK 0.005%
Alphagan P	brimonidine 0.1%	Purite
Travatan Z	travoprost 0.004%	SofZia
Xelpros	latanoprost 0.005%	Potassium sorbate 0.47%
Catioprost	latanoprost 0.005%	none
Zioptan	tafluprost 0.0015%	none
Cosopt PF	dorzolamide/timolol 2%/0.5%	none

to clean the lid. We might even try low-dose doxycycline pills—20 to 50 mg, or even 100 mg, depending on the patient's tolerance. We usually have patients on doxycycline for a few months or more. Doxycycline is useful because it pulls oil out of the lid as a side effect."

He says his practice is very diligent about teaching patients the proper way to clean their lids. "We constantly go over this with our patients," he says. "They come back, and if they're not doing well enough, we quiz them and ask them to demonstrate their technique."

Dr. Rapuano notes that "Patients' blepharitis may not be a result of chronic glaucoma medication use, but if the eyes are extra sensitive or the glaucoma medications are particularly toxic, such as those containing higher concentrations of benzalkonium chloride, then any additional help to clear up the blepharitis may be beneficial."

• ***Omega-3s.*** Dr. Salim points out that while the DREAM Study didn't find a significant benefit to using omega-3 supplements vs. olive oil placebo, another prospective, multicenter study (sponsored by Spain's Brudy Laboratories, maker of products containing omega-3s) did report a benefit of omega-3s in glaucoma patients with OSD.[1] "Supplementation of 1,500 mg of omega-3 fatty acids per day over 12 weeks reduced DED symptoms and improved Schirmer's and TBUT scores in patients on topical glaucoma drops," she says.

• ***Amniotic membrane.*** Dr. Bournias says amniotic membrane is a well-tolerated, simple approach for addressing OSD that's usually covered by insurance. "It's placed on the patient's eye and held in the fornix," he explains. "We leave it in for a few days, and after it's removed, the AM effect continues for a few weeks. It stimulates stem cells along the limbus and results in a nicer-looking cornea. Patients tend to tolerate their glaucoma drops better after AM, and their artificial tears tend to be more effective."

Bypassing the Ocular Surface

Some newer medical modalities for glaucoma and dry eye avoid the cornea altogether. "One I've been using lately is Durysta (Allergan), a bimatoprost implant that's injected into the anterior chamber," Dr. Bournias says. "It can be done at the slit lamp, and it's well-tolerated and covered by insurance. The only issue now is that it's approved as a one-time application; hopefully it'll be approved for use as an on-going treatment."

The ARTEMIS 1 study comparing Durysta to timolol reported noninferiority over a 12-week period, with up to two additional administrations at four-month intervals. "This sustained-release implant may be particularly beneficial to glaucoma patients with OSD because it can give their ocular surfaces a rest from topical bimatoprost," says Dr. Salim. "We can work toward minimizing their inflammation and improving their ocular surface during this period with preservative-free drops or even glaucoma surgery."

Tyrvaya (varenicline solution 0.03 mg, Oyster Point Pharmaceuticals) is a recently approved, twice-daily nasal spray for DED. Marjan Farid, MD, a clinical professor of ophthalmology and director of the cornea, cataract and refractive surgery program and the ocular surface disease program at UC Irvine School of Medicine, says the cholinergic agonist works by stimulating the trigeminal nerve. "This provides a pathway for parasympathetic stimulation of the entire lacrimal-functional unit," she says. "It helps the body to naturally produce all of the components of a healthy tear film and restore homeostasis.

"The Phase III studies, ONSET 1 and ONSET 2, both met their primary endpoints," Dr. Farid notes. "At the end of four weeks, they reported significant improvement in the percentage of patients who had more than 10 mm of change in their Schirmer's score, compared to the vehicle arm. They also saw a significant improvement in symptom scores in mild, moderate and severe DED patients. This improvement in symptom score was seen as early as week two in the treatment arm as compared to the vehicle. The main side effect was sneezing.

"This is an exciting new strategy for treating patients with DED," she adds. "I'm looking forward to using this more in our patients and seeing how it fits into our dry-eye algorithm."

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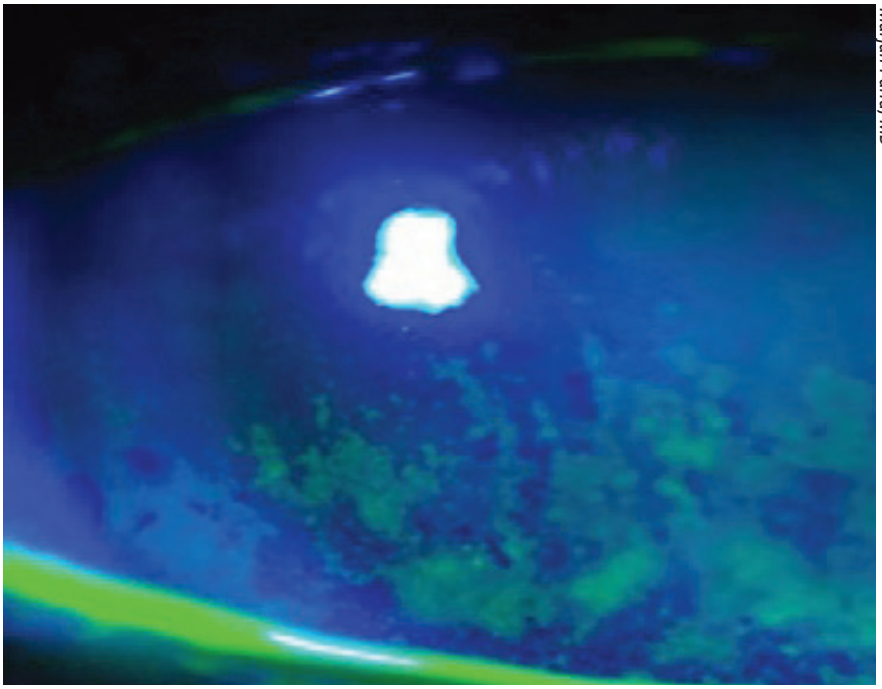

Marjan Farid, MD

Significant punctate keratitis and tear film abnormality in a dry-eye patient with glaucoma. Findings such as these are common in patients who are using topical glaucoma medications that contain preservatives.

tion and intense pulsed light are aimed at improving the patient's own tear composition, specifically the lipid layer. "Thermal pulsation involves heating the lids to express oil and improve flow, and IPL selectively ablates vascular structures to reduce inflammatory mediators' entry into the lid margin," Dr. Farid explains. "You really want to give these patients a preservative-free way of naturally stimulating their own lacrimal-functional unit. Rather than using yet another drop on the ocular surface, it's the patient's own lipid layer and improved quality of tears that are helping to restore homeostasis. Natural tears have vitamins, growth factors and more than 1,500 proteins, unlike artificial tears. Artificial tears don't restore these essential components."

Dr. Farid uses LipiFlow (Johnson & Johnson Vision) for lipid layer restoration and the TearCare System (Sight Sciences) to express meibomian glands. "I see good results with both," she says. "With TearCare, I'm able to titer the pressure to evacuate the oil glands and tailor the treatment to the patient's degree of MGD."

Laser Trabeculoplasty

"Laser treatments may be beneficial to G-OSD patients, especially if we're unable to get them off preservatives, they're on the maximum number of medications or their ocular surface is really terrible," says Dr. Rapuano. "We're always trying to reduce the drop load."

"The LiGHT trial demonstrated that selective laser trabeculoplasty is a suitable first-line treatment for glaucoma and ocular hypertension," says Dr. Salim. "After SLT, a higher percentage of patients achieved target IOP, fewer patients required glaucoma surgery and 74.2 percent of eyes required no drops at 36 months. SLT is also suitable for repeat treatments."

Dr. Bournias says he offers laser trabeculoplasty early on. "We think that by treating patients early on with SLT, they'll do better in the long term, because even if the laser trabeculoplasty doesn't work effectively over the course of five or 10 years—say they get only a one- or two-point drop—that extra 1 to 2 mmHg might be of some value over the patient's lifetime."

If SLT isn't effective, he offers ALT. "ALT isn't done as much anymore, but it's still an option," he says. "Though it's not as repeatable as SLT, it often works when SLT doesn't. I've seen this happen in many patients. The effects of ALT also seem to last longer."

MIGS

"There are several MIGS procedures available now that have great potential for reducing our glaucoma patients' drop burden and the ocular toxicity resulting from chronic drop use," says Dr. Salim. "The COMPARE study reported an average reduction of 1.6 drops after Hydrus implantation and one drop after iStent Inject implantation (p=0.004). We've also seen reports of reduced OSD symptoms after combined MIGS and cataract procedures, likely due to the need for fewer postoperative medications.

"Because of the associated reduction in drops, and thus ocular toxicity, performing MIGS earlier may help to minimize subconjunctival scarring and optimize surgical outcomes should patients need bleb-based surgery down the line," she continues. "MIGS procedures may also avoid some of the side effects associated with traditional glaucoma surgeries. If patients don't have visually significant cataract, SLT is a good alternative.

"Other surgical options that don't require concomitant cataract removal include goniotomy, GATT, Trabectome and viscocanaloplasty," she adds.

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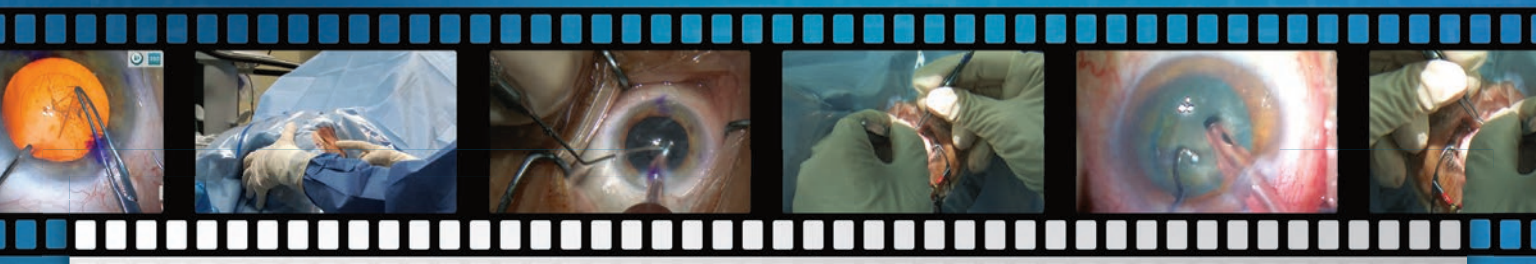

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WHAT MAKES A GOOD CHAIR OF OPHTHALMOLOGY?

There are many traits of an effective ophthalmology department chairperson: Does an NIH research grant have to be one of them?

FREDERICK W. FRAUNFELDER MD, MBA
COLUMBIA, MO.

The selection of an academic health center (AHC) chair is the most important choice a health system can make regarding the future of health care in America. Within ophthalmology, this is true whether an ophthalmologist goes into private practice or academics. It's so important because department chairs recruit and retain clinicians and scientists who train future generations of doctors, discover new cures for disease through research, and deliver high-quality clinical care from these AHC's across the country.

The ideal chair will possess a combination of traits, such as strategic thinking, communication skills and recruiting prowess, that sets him or her apart from the crowd and allows the health center to excel in its mission. One trait that's not advertised, however, is that the candidate must have external, peer-reviewed national grant funding (specifically, being a principal investigator [PI] on an R01 National Institutes of Health grant). Is this aspect of a candidate's curriculum vitae important for departmental chair leadership when weighed against a candidate's other talents?

This article briefly attempts to explain the process whereby we arrive at these hiring decisions, which traits are important, and what really goes on behind the curtain at most academic health institutions.

Traits for a Successful Chair

As the chair of ophthalmology and the dean of faculty affairs at an academic health center in the Midwest, I have a unique perspective on how AHC's recruit chairs of departments in all specialties, not just in ophthalmology. The bottom line is that good administrators have many traits in common that most of us would agree are important.

An excellent reference for data on what criteria are preferred when choosing a chair of a medical school department comes from the Association of American Medical Colleges' series on the structure of the successful medical school department chairs.[1] From data garnered from these publications, peer-reviewed literature and personal experience, I believe the following five traits are most important when selecting a chair of ophthalmology, or any other department in a medical school:

1. Proven administrative talent
2. Recruiting prowess
3. Excellent communication skills
4. Commitment to the school's mission
5. Strategic thinking ability
6. Bonus: PI on an R01 grant

To see whether my colleagues agreed, I sent out an informal survey to all the chairs of departments of ophthalmology from around the country. The following question was asked: "What are considered the top five traits (or qualifications) looked for when filling the position of a chairperson?" Thirty percent (41/134) responded, and the top five answers were vision, leadership, communication, research and

This article has no commercial sponsorship.

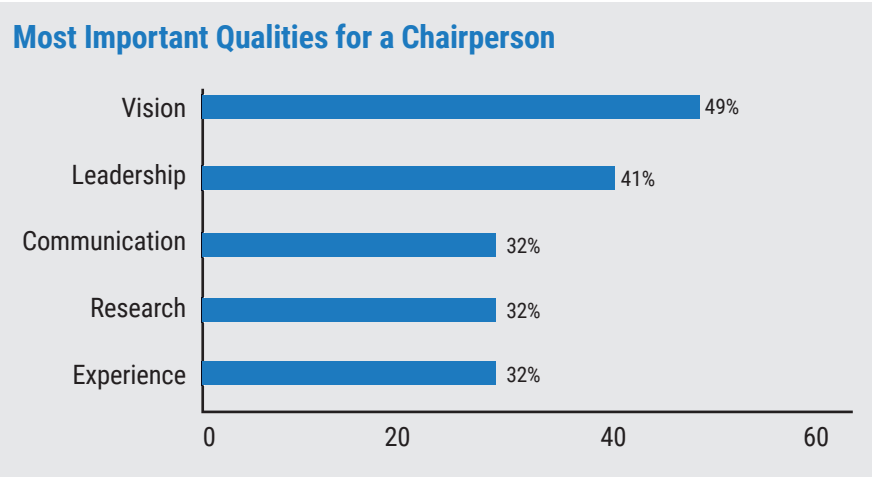
Dr. Fraunfelder is the associate dean of Faculty Affairs, and the Chair and Roy E. Mason and Elizabeth Patee Mason Distinguished Professor of Ophthalmology at the University of Missouri.

experience. A fascinating omission was the requirement that a chairperson have an NIH grant. In fact, from the 41 returned surveys, only two even mentioned a grant. There were 24 total traits suggested by chairs of ophthalmology and number 23 by frequency of answers, was "needs an NIH grant." A grant was suggested twice in the 41 responses and wasn't in the top five in any instance.

But what makes the traits enumerated above so important for a chairperson? Each of the preferred chair characteristics mentioned above deserve some explanation:

• ***Proven administrative talent.*** Administrative talent is probably learned over time and comes with successes and failures over the course of many years. I tend to think there are very few natural born leaders. Instead, it's more like a process of iron sharpening iron—the metal is tested over time and gets better. This is often observed in our peers as we become more patient, kind, emotionally in tune with our faculty, and communicate more effectively as we mature into our jobs. It's a truism that many of us go into the job having very little idea of how to run an academic ophthalmology department, but in the end we either learn and get better or we're let go. Even so, this trait is of paramount importance in a leader and it's under-recognized in my experience. Leaders at all levels should create a system whereby they're looking for this trait. In a way, it encompasses all the other important traits of a departmental chair.

• ***Recruiting prowess.*** A chair of a department has two main jobs: set the strategy and vision for the department and recruit well. This latter trait can't be overstated. If chairs are the lifeblood of medical school leadership, then the faculty they recruit are the lifeblood of the entire school. Research, teaching and clinical care flow from these recruits and a chairperson has to make this a top priority. If a chair isn't good at recruiting, they need to get good at it. They should talk to their peers, go to training courses, engage with the AAMC and recognize it as vital to both their and the school's success. There's no excuse to not recruit effectively if you're a chair. *(For an in-depth discussion on recruiting faculty, see "Confessions of a New Chairman on Recruiting" in* Review*'s April 2016 issue.)*



The most popular answers chosen from a sample of 41 chairs of ophthalmology from around the country. The percentage is the proportion of the respondents who identified that quality as being in the top five most important traits.

• ***Excellent communicator.*** This is an obvious trait for a leader at any level. What's important to point out here is that good communicators are good with a variety of audiences. A good chair is good one-on-one, one-on-five and one-on-100. They know their audience and never talk down to them. They're upbeat, encouraging, positive and moving forward almost always. When faced with challenges, they're able to convey empathy, compassion, a we-will-fix-this attitude and they'll talk to all stakeholders involved.

One key to communication is repetition. You don't just send out an email; you send out an email, talk to the group, talk to each individual and then send out the email again. It's like wearing a belt with suspenders—but you make sure your pants are also tight.

Communication skills are encompassed in the first trait, being an administrative talent. This skilled is honed over time and is cultivated over many years of trial and error.

• ***Commitment to the school's mission.*** This concept may sound obvious, but I don't think it is. Many of us can recite our mission statement from memory, or can at least look it up quickly. The concept here is that it's more than just teaching, research and service. The idea is that the leader is committed to something greater than themselves: Did they join the Navy to see the world or did they join the Navy so the world could see them, so to speak? Individuals who adopt the values of their institution are easy to trust, follow and understand. In other words, are they loyal to the mission of the school or are they loyal to a variety of other options (possibly even loyal only to themselves)? Commitment to the mission of the medical school is vital in choosing a department chair.

• ***Strategic thinker.*** This final trait encompasses many qualities that are important in a chair. If you're a strategic thinker, you'll develop emotional intelligence, build an inclusive and diverse department,

shore up your weaknesses, learn the financials you aren't familiar with and address in a logical way the challenges that so many of us face at an AHC. This type of leader has a high IQ and will learn what's necessary to become successful and remain so. Seeing the forest for the trees while also understanding the tree itself is a good way to think about this kind of leader. So many times, our chairs don't see the problems, or remain aloof from them. It's possible they simply don't understand the problem. Setting strategy and vision is "job one" of a department chair.

All ophthalmologists trained in the United States have experience with the chair of the department during their training. We learned our clinical and surgical skills under the tutelage of our faculty mentors, who were recruited by our chair. We subsequently go out into the world and open our own practices, join a practice or join a university of our own choosing. How a department chair is chosen is important to all of us regardless of the nature of our ophthalmology practice, now or in the future. Our future colleagues will be shaped by these decisions at our medical schools.

The Determination Process

Now that you've got a sense of the traits of a successful chair, it's time to discuss how universities evaluate these traits and choose a chairperson.

The selection process is similar at most universities: The dean of the medical school identifies the need, a job posting is distributed nationally, a diverse search committee composed of leaders and stakeholders from within the university is formed, a "dean's charge" (more on this later) is performed, applicants are screened by the committee, multiple rounds of interviews take place, negotiations ensue and, finally, a new chair is announced. Though this sounds relatively straightforward, there are aspects of the process that aren't readily evident.

First, the university's president/chancellor, or similar leader, has a lot to say about the candidate. They convey this strategy to the dean of the medical school. Though the vision and strategy of our leaders is important, university presidents are rarely physicians, and many times aren't familiar with the culture of medical schools. Because of this, the relationship between a medical school and the university it functions within can be described with one word: misalignment. While it's acknowledged that there are many different types of governance models at AHC's, and some medical schools operate independent of the university management, misalignment is a common theme between institutional leaders of universities nationwide and an unfortunate reality within almost all AHC's. To quote the father of all management gurus, Peter Drucker, "AHC's are the most complex management organizations."[2] (He didn't mean this as a compliment.)

At some point during the search for a new chair, the dean will meet with the search committee and convey what he feels is most important when choosing a new department chair in a process called the "dean's charge." The charge consists of factors he considers important, which may include some of the traits described above, as well as other ones. The dean is in constant communication with the many layers of governance at the university, including presidents, chancellors, vice chancellors, provosts and other leaders, and brings this perspective to the search committee in the form of a "charge"—as in "Go forth and don't mess this up."

Also, in the process of making his charge, the dean emphasizes confidentiality, indicates who makes the decision on hiring (presumably the dean or a designee), and that the search committee is advisory in nature. One would hope that the dean would say what is almost always implied: "This institution will only consider candidates for the chair of the department of ophthalmology if they are a PI on an R01 NIH grant that they can bring with them to our medical school." Having been a part of multiple search committees at more than one institution, I can tell the reader with assurance, this charge is almost never uttered. The irony here is that, despite all the important traits we've already discussed, the presence of an NIH grant is, in many cases, the most important issue for the president or chancellor of the University. In stand-alone medical schools, it may even be the number one priority of the dean. Why is that?

NIH grants, and other types of external peer-review grants (e.g.,

Department of Defense grants), can lead to tremendous discoveries in the treatment of disease. We're lucky that our country values research and supports researchers in this way, and this is what sets AHCs apart from other types of healthcare organizations. NIH grants bring not only financial support to the university's research mission, but also tremendous recognition and prestige to the school. A chair of a department in a medical school will probably better understand their PhDs and their MDs who are clinician scientists if the chair has experience with this type of funding for research. NIH grant numbers at a university are also a quantitative way university presidents can compare themselves to each other. A leader is allowed "in the club" so to speak if their school is particularly prodigious in this area.

However, looking at the numbers, an over-emphasis on grant funding may be short-sighted. According to published data, there are 2,824 academic ophthalmologists at U.S. medical schools.[3] Only 175 clinician scientists receive federal funding in ophthalmology.[4] This means if leaders are choosing a chair of an ophthalmology department who must be a PI on an R01 NIH grant, the pool consists of only 6 percent of all academic ophthalmologists. Unfortunately, this is a very small subset of talent and will exclude many of the top five traits described earlier in the article.

Furthermore, only about 4 percent of clinician scientists who had R01s appeared to have maintained continuous funding, with half of them having not received additional R01 funding 10 years after receiving their first R01.[5] Is this because so many of these clinician scientists become department chairs and no longer have time for research? It leads to the question: Is this model of choosing chairs as R01 grant-holding individuals a good strategy if half are not going to receive funding in the future and very few maintain continuous funding throughout their careers? Are university presidents chasing fool's gold? Once a clinician scientist takes the mantle of administrating the complexities of a large ophthalmology department, is there still time for their research? It's difficult to know the answers to these questions. Suffice it to say, some individuals seem to be able to "do it all" and the world is a better place because of their abilities. Still, from the data, it's clear not everyone can do that. If they did, there would not be this huge drop off in research productivity after a clinician scientist becomes a chair of an ophthalmology department.

Unfortunately, if one is an administrative talent but isn't a PI on an R01 NIH grant, they may not be considered for leadership as a chair of a department. The data on the prevalence of NIH grant-holding chairs can be gathered from the NIH website (https://report.nih.gov/). There are 131 ophthalmology department chairs in the United States and 50 have had, or used to be a PI on, an R01 NIH grant within the past five years (38 percent). Only 24 (18 percent) currently are the PI on an R01 NIH grant.

From this, it appears that close to 40 percent of chairs have, or have had, grant funding and are the PI on an R01 NIH grant. Clearly, there are a number of very good chairs who don't have grants and a number of very good chairs who do. The point I'm trying to make is that using just one trait as a litmus test for choosing a department chair is unwise. It's up to us as healthcare leaders, faculty, scientists and/or clinicians in private practice who are alumni of an AHC to communicate this to our presidents, provosts, chancellors and other stakeholders in order to avoid that aforementioned institutional misalignment.

Ophthalmology chairs should have proven administrative talent, recruiting prowess, excellent communication skills, a commitment to the mission of our schools and be strategic thinkers. This is who we want to help lead our profession and who we want working alongside us as ophthalmologists, regardless of whether we choose academics or private practice after graduation from our residency program. It's incumbent on us as ophthalmologists to convey the importance of these traits to our leaders. A PI of an R01 NIH grant is the cherry on top, but not the sundae. Our failure to communicate about this could lead to misalignment.

An administratively talented chair has the ability to create a vision and strategy, build teams around this vision, and then facilitate the process of growth in the missions of excellent clinical care, research and teaching. They do this by effectively recruiting and retaining talented faculty. If the chair has these traits, they know their own strengths and weaknesses. For instance, if the chair isn't strong in research, but is administratively talented, they'd recognize this and appoint a competent research director.

It's my hope that the future of health care in America is populated by chairs who minimize misalignment by possessing such leadership traits, with grant funding being a nice, but not necessary, bonus. ◀

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Point: Use of MicroPulse TLT Should Be Expanded

Data suggests this technology could benefit many relatively healthy eyes, not just those with advanced glaucoma.

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MicroPulse TLT is a great tool to have in your armamentarium for treating glaucoma. Prior to the advent of MicroPulse, if your patient had advanced glaucoma, the main treatment options were trabeculectomy or a tube, surgeries that are fraught with postop complications and often require frequent postop care. (The advent of minimally invasive glaucoma surgeries, or MIGS, has provided another option that involves less follow-up, but MIGS procedures are largely utilized in early glaucoma.)

The current version of MicroPulse is a great tool for several reasons: it's effective; it's easy to do; it requires minimal procedural training; it's portable; and it requires much less postop care than a trab or tube. The complication rate is very low and postop pain is generally negligible. It's a quick procedure that's easy to fit into your schedule. It only takes a couple of minutes, and there's no prepping or draping. You don't need an OR or even an operating microscope to perform the procedure. (In fact, the portability of this technology has made it widely used in many other countries; I often get questions about it from colleagues in Africa and the Middle East.)

Currently, most surgeons reserve MicroPulse for the treatment of eyes with advanced glaucoma—eyes in danger of losing most or all vision—as well as eyes that are already blind. Here, I'll discuss the MicroPulse technology and how the procedure is currently performed, and share some of the data that supports the idea that it should be an option for treating much-less-damaged eyes as well.

The Technology

The current version of this treatment is referred to as micropulse transscleral laser therapy, or MP-TLT. The earlier form of this laser, called diode transscleral cyclophotocoagulation (TSCPC) was designed to partially destroy—or at least decrease the function of—the ciliary body, using thermal energy. This effectively lowered the rate of aqueous production. It was historically reserved for end-stage or blind eyes, because the destruction caused widespread damage and inflammation. Complications sometimes included phthisis (very low intraocular pressure, causing shrinking of the eye); inflammation inside the eye; sympathetic ophthalmia (inflammation in the other eye); hypotony; and occasionally, chronic pain following the procedure. These severe complications made TSCPC a treatment that most practitioners reserved for severe, end-stage glaucoma patients with poor visual potential.

MicroPulse was developed in the 90s to perform focal laser for macular edema. The idea was to affect the ciliary body while minimizing damage to the adjacent structures. While the earlier cyclophotocoagulation technology applied the laser as a continuous wave, MicroPulse is essentially a subthreshold laser that chops the continuous-wave pulse into short pulses. This allows the tissue to heat and cool and heat and cool, preventing the thermal ramping-up that leads to increasing temperature and tissue destruction. Multiple studies, done both *in vivo* and on cadaver eyes, have demonstrated that this results in minimal changes to the adjacent tissue.

The current version of MicroPulse uses a 31.3-percent duty cycle, which means that 31.3 percent of the time the laser is being administered; the remainder of the pulse, the laser is off. This translates to 0.5 milliseconds of "on" time and 1.1 ms of "off" time, using one-third as much energy as when the laser is applied in a continuous wave.

This version of the laser causes far fewer adverse effects than the continuous wave treatments. There are minimal changes to the tissue surrounding the ciliary body, compared to TSCPC. A temporary mydriasis can happen, but sympathetic ophthalmia and phthisis are virtually never reported. Overall, it's clear from the literature that severe complications are very uncommon with this version of the technology.

Unresolved Questions

There are still some issues being

(Continued on p. 56)

This article has no commercial sponsorship.

Dr. Singh is a professor of ophthalmology and chief of the Glaucoma Division at Stanford University School of Medicine. **Dr. Netland** is Vernah Scott Moyston Professor and Chair at the University of Virginia in Charlottesville.

Counterpoint: Expanding MPTLT Use is Premature

Despite showing promise, there are a number of reasons we shouldn't be too quick to use this technology on healthier eyes.

IAN P. CONNER, MD
PITTSBURGH

I'm well-acquainted with the MicroPulse procedure; I use it for many of my patients. In fact, my personal opinion is that we probably don't use it as often as we should. However, it's still a relatively immature technology; there's still a tremendous amount that we don't know about it. For that reason, I see plenty of reason to exercise care when considering expanding its use.

Here are several reasons we should proceed with caution.

• ***We're still not sure how it works.*** It's true that MicroPulse has been shown to cause minimal changes to adjacent tissue—a significant advantage over previous modalities. However, as Dr. Sieminski has noted, what's actually causing the lowering of intraocular pressure remains unclear. Rushing to use a procedure in patients who may not be in danger of going blind from their disease—such as patients with earlier-stage glaucoma—is a questionable premise when we don't even really know how the procedure works.

It's one thing to treat patients with a poorly understood technology if we know they're going to go blind unless we do something. This rationale is often used in other medical areas such as oncology; when we've tried everything that we understand and nothing has worked, then we try experimental protocols. Some would argue that expanding the use of MicroPulse to include early glaucoma patients or glaucoma suspects is a little bit like uncontrolled experimentation.

• ***The ideal parameters for different eyes haven't been determined.*** Because we don't really understand how it works, we don't know what the optimal parameters are, in terms of the amount of energy being applied, how long we should apply it, the length of each pulse and how fast we should sweep the probe across the eye. Working out these parameters with patients who have very mild disease raises some ethical concerns.

• ***Even "minor" side effects can be a big deal to a patient with good vision.*** My experience confirms Dr. Sieminski's point that side effects of MicroPulse treatment are limited. More severe complications like phthisis, corneal edema and hypotony are very rare, and that can be seen as an argument for using MicroPulse in a broader swath of patients. However, potential complications like cataract progression, transient macular edema and uveitis are still concerning in a patient with mild disease. Yes, issues like secondary cataract formation have also been reported with alternative treatments such as trabeculectomy in the past, but any loss of vision in a patient with good vision is worrisome. Likewise, having temporary mydriasis and blurry vision—which we don't have a good treatment for, and which can last for months after the procedure—is not a benign condition, so we should think twice about subjecting patients to that.

If we're going to use this treatment in patients with much milder disease, we need to think hard about these potential complications. We may consider them to be mild, but the patient might not agree. (At the least, we need to make sure that the patient understands that this is a possibility in the consenting process.)

• ***Many of the studies supporting the expansion of MicroPulse to less-sick eyes are retrospective.*** It's true that increasing numbers of papers are being published about using MicroPulse to treat different kinds of glaucoma. However, almost all of this data is retrospective. A surgeon, for example, may decide to start using MicroPulse to treat patients with pseudoexfoliation or uveitic glaucoma, and then publish the results.

Unfortunately, there's a huge selection bias at play in this kind of study. These are not rigorous, controlled trials. In fact, it's very uncommon for anyone to publish negative data from a series of patients treated with the expansion of a clinical device or procedure; there's a bias toward publishing cases with good outcomes. For that reason, we need to be cautious about basing our decisions on retrospective data.

It's reassuring that people are doing this and getting good results, but right now it's far from a scientific certainty that expanding the indications for this treatment is a safe thing to do.

• ***We don't know much about repeating MicroPulse treatments.*** The idea that patients might need more than one treatment is some-

(Continued on p. 57)

CONTINUOUS WAVE TRANSSCLERAL CYCLOPHOTOCOAGULATION VS. MICROPULSE TRANSSCLERAL LASER THERAPY

	CW-TSCPC	MP-TLT
Energy level	High energy	~1/3 the energy of CW-TSCPC
Overall impact on tissue	Full-thickness ciliary muscle necrosis	Minimal histological findings (minor coagulation)
Impact on ciliary epithelium	Destroys pigmented and non-pigmented ciliary epithelium	Does not destroy non-pigmented epithelium
Mode of action	Inhibits secretory activity of the ciliary epithelium	Unlikely to inhibit secretory activity of the ciliary epithelium; however, mode of action is multi-factorial. Increased uveoscleral outflow presumed dominant mode of action
Typical usage	Typically reserved to lower IOP in eyes with poor visual potential	May be used in eyes with good vision
Glaucoma severity	Treatment of choice for blind, hypertensive eyes	Broad range of glaucoma types and severity
Adverse events	Typically associated with a high incidence of adverse events	Low incidence of significant adverse events. Most common, temporary mydriasis
Target area	Target: pars plicata – 1.2 mm posterior to the limbal margin	Target: pars plana – 3.8 mm posterior to the limbal margin

Unlike the earlier continuous-wave laser, which was designed to partially disable the ciliary body via thermal energy, the MicroPulse Transscleral laser achieves a lower IOP while only causing minimal tissue damage. The mechanism of action remains unclear.

MicroPulse Use Should Be Expanded

(Continued from p. 54)

resolved. Because the tissue doesn't heat up as much and cause obvious damage, it's a little harder to explain why MicroPulse is effective at lowering IOP. The lower energy doesn't completely inhibit the secretory activity of the ciliary epithelium and ciliary body, which suggests that there must be other ways in which it works to lower eye pressure.

There are multiple theories that attempt to explain what the laser energy is doing that ends up lowering the IOP. One theory is that it causes inhibition of secretory activity, much like TSCPC, but to a lesser degree. Other proposed theories include that MicroPulse increases uveoscleral outflow, and that it has a pilocarpine-like effect, which increases the trabecular outflow due to a posterior displacement of the scleral spur.

It's not yet clear if one of these explanations is more correct than the others, but it's possible that all of these mechanisms are working together. If this turns out to be true, then a MicroPulse treatment could be seen as similar to a combination glaucoma drop—increasing uveoscleral and trabecular outflow, while decreasing aqueous production.

Another issue that still needs to be resolved is refining the variables involved in applying the treatment. Three main variables can affect the impact of the procedure: the total power used, the total duration that laser is applied to the eye, and the velocity at which the laser is swept over the tissue ("dwell time"). The importance of the last factor can be compared to sweeping your hand over a lit candle: If you do it quickly, the impact on your hand will be minimal, but if you move your hand over the candle very slowly, you'll get burned. I'm very interested in adjusting these variables to help understand what will make the surgery more efficacious.

Unfortunately, many studies involving the current MicroPulse procedure don't report the amount of time spent in a given quadrant or hemisphere, and even fewer report the sweep velocity or dwell time. These factors haven't been on people's radar as important variables; surgeons tend to think that if the patient's glaucoma is more severe they should simply increase the power. We're not routinely considering variables such as pigmentation of the ciliary body—or as a correlate, trabecular pigment—or the exact positioning of the ciliary body. This is one reason the ideal parameters for use remain to be determined.

How I Use It

Although MicroPulse can be used outside of the OR with minimal anesthesia, I tend to use it in the OR because I find it makes the procedure technically easier, and it's more comfortable for the patient. I want to be precise about the orientation and the timing of my sweep to ensure the effectiveness of the procedure. It's undesirable to have the probe sliding anteriorly onto the cornea or posteriorly due to patient movement, because you can inadvertently treat the incorrect area. (Doing so probably wouldn't hurt the eye, but it could make the treatment less effective.) Therefore, I prefer to do this in a controlled setting like the OR, and sedate the patient a fair amount.

I know that some surgeons are able to perform this procedure in the office using retrobulbar anesthesia, but in my early cases under Monitored Anesthesia Care (MAC) anesthesia with a retrobulbar block, I found my patients were stimulated by the laser, causing them to move intraoperatively. I currently use a strong "cocktail" of IV anesthetics, including propofol and ketamine, which adequately sedates the patient and has eliminated the need to do a retrobulbar. One advantage of this technique is that I don't need to patch the patient post-procedure.

My typical protocol when using the new handpiece is a power

(Continued on facing page)

Expanding MPTLT Use is Premature

(Continued from p. 55)

thing we have to mention in patient consent forms, because up to half of the patients treated with MicroPulse require a retreatment at one year. So this is far from being a "one-and-done" treatment.

This is reminiscent of selective laser trabeculoplasty. When we treat patients with SLT, a certain proportion of them will need retreatment within a relatively short amount of time. However, SLT has been around for so long that we have a really good handle on the nearly nonexistent side effect/complication profile. As a result, we feel comfortable treating people with early disease using SLT—and treating them more than once or twice if we have to. In contrast, with MicroPulse, we have some data about treating patients once, but have almost no published data about patients who are treated two or three times.

The reality is, we just don't know what the potential ramifications of multiple treatments might be in patients with good vision and mild disease. So it's not necessarily reassuring to say that we can just repeat the laser if the effect wears off after a short period of time.

Caution is Warranted

All of these points have to do with the uncertainty of a relatively new procedure. Most of us are pretty comfortable offering new technologies with uncertain side-effect profiles in patients who are in dire need of treatment, but we should be a little more cautious about patients who aren't likely to lose their vision.

Certainly there are circumstances in which MicroPulse compares favorably to other options. For example, I agree that patients who are post-keratoplasty have limited alternate options for controlling their IOP. The graft causes the glaucoma, but then many options for treating the glaucoma—for example, placing a tube in the eye—lead to graft trauma and/or failure, which is pretty devastating. However, even in this situation the use of MicroPulse warrants some caution because we don't have a lot of data; we don't know what's going to happen to these grafts over the long term. Use of MicroPulse in children also appears to be possible, with the data so far suggesting no significant complications in the short term. But these patients may live for another 50 or 70 years, and we have no way of knowing what we may be signing them up for in the future. That data doesn't currently exist.

In reality, MicroPulse is probably not a procedure for everybody. Whenever a new technology appears, there's always a lot of initial enthusiasm. Then, as time goes by and we use it in our patients and published data appears, we start to whittle down the indications. Today, for example, I can list 19 specific criteria that I really like to be in place before I do a trabeculectomy. If the patient checks all of those boxes, I feel confident he or she will do really well; if not, then I have a sinking feeling the surgery may fail, because we know that about 50 percent of trabeculectomies fail within 5 years, no matter who does the surgery. But we're nowhere near that level of understanding when it comes to MicroPulse.

This is a story that gets repeated over and over. We want a magic bullet, and we have a lot of hope that whatever the newest thing is might be that bullet. Then, as we use it, we find that it works really well in some patients, but patients have to have specific criteria to fall into that group.

MicroPulse will clearly have a place in our glaucoma armamentarium, but it will take some time to clarify exactly what that place should be. ◂

ABOUT THE AUTHOR

Dr. Conner is an assistant professor of ophthalmology and bioengineering at the University of Pittsburgh. He serves as the chief of ophthalmology at UPMC Shadyside and the UPMC glaucoma fellowship director. He reports no relevant financial ties to anything discussed in this article.

(Point, continued)

setting of 2,500 mW, spending 50 seconds per hemisphere, and 20 seconds per sweep. (I routinely note these factors in my operating log for future reference.) I don't like to use a lid speculum during the procedure, because I find that the MicroPulse handpiece can get hung up on the speculum and impede the sweeping motion. I find that the newer MicroPulse handpiece is effective at pushing the eyelid out of the way.

Patients for whom I find MicroPulse particularly useful include:

• ***patients who've had prior glaucoma surgery,*** such as an ExPress shunt, or a tube or trabeculectomy. When a patient already has a tube shunt and is still progressing, one option would be to implant a second tube, but most glaucoma specialists will tell you that a second tube is not their favorite option, because there's already significant hardware in the eye. MicroPulse has been a great adjunct for patients in this situation.

• ***patients who are poor incisional surgery candidates.*** This would include those in a nursing home, those who aren't cooperative, and any patient whose circumstances cause you to be concerned about infection.

• ***patients in whom there's good reason to want to do both eyes at the same time.*** MicroPulse can treat both eyes in a single surgery without any additional risk or lesser outcome. For example, if I'm doing an exam under anesthesia and find both eyes have high pressure, I can

(Continued from p. 56)

simply treat both eyes and be done. (I put this possibility in my consent form.)

Of course, MicroPulse does have limitations. For example, given that MicroPulse is a good adjunct to an existing tube shunt, one might wonder whether it could be used instead of a primary shunt. A recent paper asked this question, comparing MicroPulse to initial Ahmed valve placement.[1] At 12 months, 73.3 percent of those in the Ahmed group had pressure lowered by 30 percent or more; this level of pressure-lowering was only achieved in 33.3 percent of patients receiving MicroPulse. The number of drops being used was reduced significantly in both groups, but was reduced more in the Ahmed valve group. Half of the eyes in the MicroPulse group were referred for additional treatment because of acute postoperative IOP rise, while no further procedures were necessary in the Ahmed shunt group. So according to this study, MicroPulse wouldn't be best initial treatment option if a tube is a possibility.

Starting Cautiously

As noted, most surgeons currently reserve MicroPulse for end-stage, refractory eyes. In fact, the first two studies of this technology were conducted on patients with refractory glaucoma by Paul Chew, MD, and Maria Aquino, MD. The first study treated 38 patients with refractory glaucoma. It found a success rate of 80 percent—defined as a final IOP between 6 and 21 mmHg or a 30 percent IOP reduction—at final follow-up.[2] No patients experienced hypotony or vision loss. Seven patients (18 percent) reported mild pain on postop day one, but the remainder reported no postop pain.

The second study involved 48 patients with refractory end-stage glaucoma that were randomized either to continuous-wave treatment (TSCPC) or micropulse.[3] The micropulse did better in terms of success rate (52 percent vs. 30 percent at 18 months). Mean IOP was reduced 45 percent in both groups, but the complication rate was higher with the continuous wave treatment.

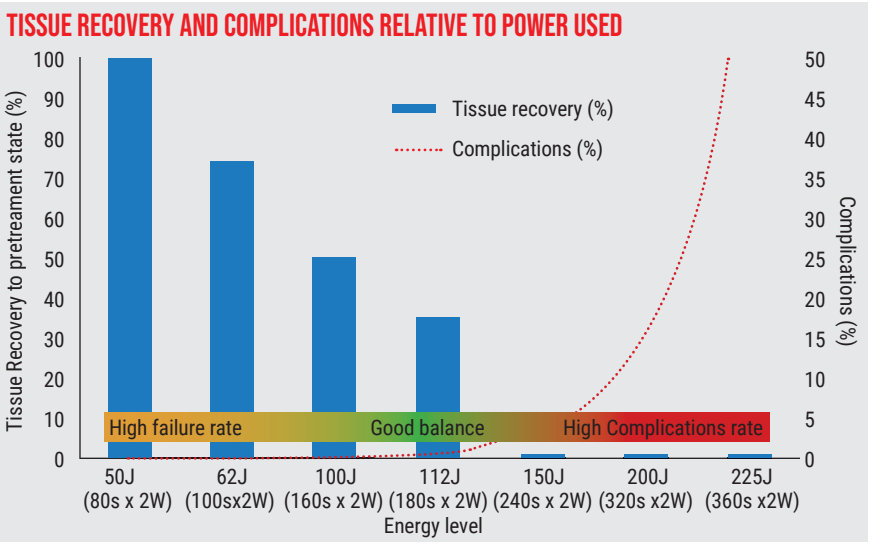
Initially, like many surgeons, I reserved use of this procedure for patients who were not ideal surgery candidates and patients who needed to have both eyes treated at the same time. Gradually, however, I began trying it on a broader range of patients, with some success. I discussed my broadening criteria for treatment—treating patients with good central vision—with my colleague Syril K. Dorairaj, MD, from the Mayo clinic in Jacksonville, Florida. After comparing our criteria we decided it might be worth looking at both sets of data.

We pooled our data and looked at the MicroPulse patients who started with 20/40 vision or better.[4] (Our laser settings and techniques were similar.) We looked at patients out to 12 months and found significant IOP-lowering and reduction in use of medications. On the downside, 12.5 percent of these individuals, at final follow-up, had lost two or more lines of vision. Those experiencing this outcome were not random, however. A majority of these patients were phakic, and the data suggested that the vision loss was attributable to cataract formation. My take-home was that this laser should be used with caution in phakic patients due to the risk of cataract formation. (It's worth pointing out that if a patient has advanced glaucoma and the alternative is a trabeculectomy, the patient is also likely to get a cataract from having that procedure.)

In terms of potential complications, published studies reveal that chronic uveitis, cataract formation and macular edema are seen in some patients.[5,6] On the other hand, I haven't observed phthisis, corneal edema or persistent hypotony in my experience. (Some of the studies that do cite these complications used pretty high levels of laser energy.)[5,7,8]

Expanding the Scope

Today the indications for MicroPulse are broadening even further. Our group's retrospective 2019 study demonstrated that MicroPulse was effective and relatively safe in patients with good central vision.[4] In addition, many other papers have



Ideal parameters for MicroPulse are still being worked out. This study showed that at low energy levels, need for retreatment is high, while at high energy levels, complications increase dramatically. (Sanchez et al, 2018)[8]

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described using MicroPulse to treat different kinds of glaucoma, including open-angle glaucoma, exfoliative glaucoma and uveitic glaucoma. The published data indicate that it's safe and effective for many different kinds and stages of glaucoma. In short, the evidence is mounting that this is not something that needs to be relegated only to people who have poor visual potential.

A few examples:

• A retrospective study published in 2020 looked at the outcome of using MicroPulse on 342 eyes of 214 patients with a wide spectrum of glaucoma-related issues, including ocular hypertension, all severity levels of glaucoma (including eyes with good vision and treatment-naïve eyes), and all types of glaucoma, include normal-tension glaucoma.[9] At one year, 67.8 percent had achieved a 20-percent-or-greater IOP reduction. The data showed that the amount of IOP reduction was greater when the starting IOP was higher, and the chosen laser power setting also correlated with the amount of IOP lowering. (IOP dropped an average of 31.5 percent with the laser power set at 2,500 mW or more, and 17.8 percent when the power level was less than 2.500 mW, $p<0.02$.) No patients demonstrated persistent inflammation or hypotony, phthisis bulbi, or sympathetic ophthalmia. Interestingly, the mean number of topical glaucoma medications was unchanged from baseline to one year.

• Also in 2020, Rob Noecker, MD, and colleagues reported on a retrospective study looking at 95 patients with various types of glaucoma who were refractory to topical drops and poor candidates for incisional surgery.[10] Mean preop IOP was 25.1 ± 5.3 mmHg; mean postop IOP at 12 months was 17.5 ± 5.1 mmHg ($p=0.004$). Mean number of medications dropped from 3 ±1.1 preop to 1.4 ±1 at one year ($p=0.03$). Seventy-three patients (77 percent) achieved success with one treatment; the remaining patients achieved significant IOP-lowering after one to four additional treatments. There were no instances of prolonged intraocular inflammation or long-term hypotony.

Special circumstances such as glaucoma in post-keratoplasty patients and pediatric glaucoma have also been studied with MicroPulse:

• A 2019 retrospective study of 61 post-keratoplasty eyes of 57 patients that had received MicroPulse treatments (31 eyes received a single treatment; 21 received two treatments; eight eyes receive three; and one eye received four treatments) found that it reduced mean IOP significantly out to one year.[11] Six eyes (10 percent) received subsequent glaucoma filtration surgery. Notably, graft survival was 94 percent at one year and 81 percent at two years after the initial laser treatment.

• A prospective study published in 2019 included 45 eyes of 36 children requiring TS-CPC; it compared the outcomes of MicroPulse vs. continuous-wave applications.[12] Success was defined as an IOP of 5 to 21 mmHg at six months, with no vision-threatening complications. IOP reduction was 63 percent in the MicroPulse group and 67 percent in the continuous-wave group. The success rate was higher in the MicroPulse group (71 percent vs. 46 percent), but the difference wasn't significant. However, while no significant complications were noted with MicroPulse, one eye in the continuous-wave group developed phthisis bulbi, and two eyes had severe pain and uveitis.

Into the Future

It's true that much remains to be determined regarding how best to use this technology. We still need more prospective trials to determine what the most effective settings for patients are. Furthermore, we need standards for the sweep velocity, which may have a significant impact on how effective the treatment is. We could even consider applying the treatment in discrete spots, similar to TSCPC, to standardize the application further. And, we have yet to determine what types of glaucomas are more successfully treated with MicroPulse and what types of patients have better IOP-lowering (patients with prior glaucoma surgery, or those who haven't had glaucoma surgery). These are questions we need to work on, to standardize the dosage and help everyone use this procedure more effectively.

Nevertheless, our experience, and that of many other surgeons, suggest that this technology could be benefitting far more patients than it currently is. I hope that other surgeons will help to expand these horizons. ◂

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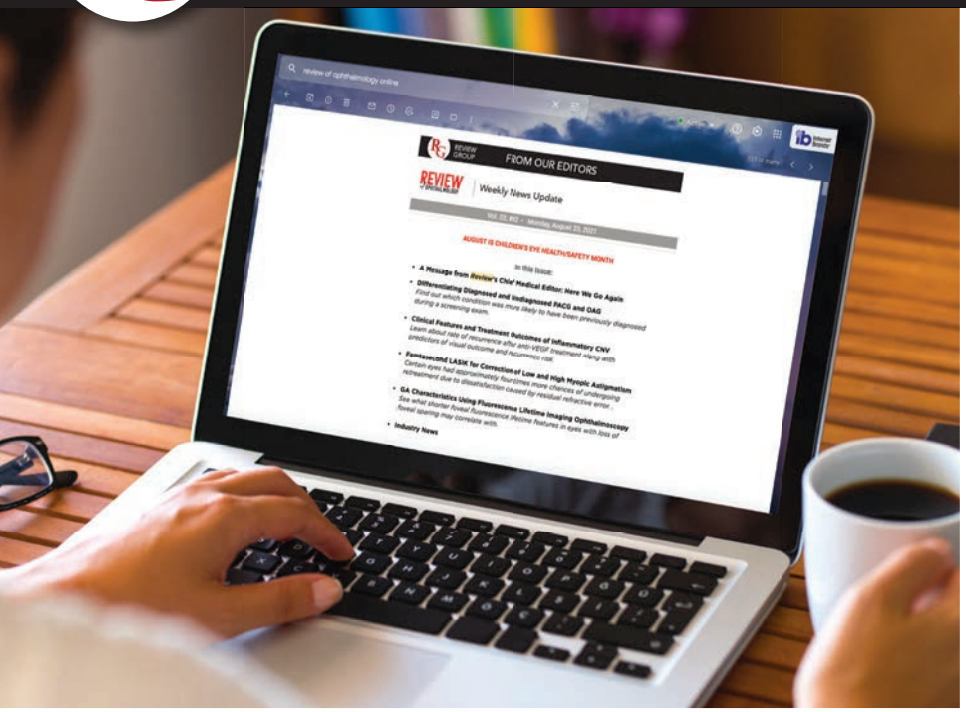

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REVIEW GROUP — FROM OUR EDITORS

REVIEW of OPHTHALMOLOGY — Weekly News Update

Vol. 22, #32 • Monday, August 23, 2021

AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

- **A Message from *Review*'s Chief Medical Editor: Here We Go Again**
- **Differentiating Diagnosed and Undiagnosed PACG and OAG**
  Find out which condition was more likely to have been previously diagnosed during a screening exam.
- **Clinical Features and Treatment Outcomes of Inflammatory CNV**
  Learn about rate of recurrence after anti-VEGF treatment along with predictors of visual outcome and recurrence risk.
- **Femtosecond LASIK for Correction of Low and High Myopic Astigmatism**
  Certain eyes had approximately four times more chances of undergoing retreatment due to dissatisfaction caused by residual refractive error.
- **GA Characteristics Using Fluorescence Lifetime Imaging Ophthalmoscopy**
  See what shorter foveal fluorescence lifetime features in eyes with loss of foveal sparing may correlate with.
- **Industry News**

A message from *Review*'s Chief Medical Editor, Mark H. Blecher, MD: Here We Go Again

I am, like most of you, totally over COVID. But as the cliché saying goes, "COVID isn't over us," which was mildly funny until it wasn't. We had a small happy window of normalcy this spring when marginally successful vaccinations caused the infection rate to plummet. The sun started to shine again ... and then it was gone. The smug satisfaction the vaccinated among us enjoyed was

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Managing CME After Cataract Surgery

(Continued from p. 41)

priate to have a quick conversation to explain that they're at higher-than-average risk of CME, and tell them why," says Dr. Arepalli. "You can explain that if it occurs—which is possible even when the surgery goes perfectly—it could prevent them from reaching their ideal vision, and you might have to send them to a retina specialist. It's a good way to set realistic patient expectations."

Dr. Lin agrees. "I explain that it can continue for six months, in some cases up to a year," she notes. "I emphasize that we're typically able to get it under control. It's not something anyone will have to deal with for the rest of their lives."

"Also," Dr. Arepalli adds, "make sure they understand that if CME occurs, it's not your fault. Patients in the cataract surgery age range usually have friends whose cataract surgery left them with 20/20 vision on day one, so they'll be frustrated if their postop course is longer and more complicated. You don't want the patient to think that postop CME means you did something wrong during the surgery."

• ***If you find CME, do a very thorough work-up.*** "I've seen patients present for a pseudophakic CME evaluation and it turns out to be something else," says Dr. Arepalli. "Of course it is inflammation, but it may turn out to be associated with an underlying condition that should be treated. In one patient the problem turned out to be sarcoidosis; they needed systemic immunosuppression to quiet it down permanently. I've caught anterior chamber cell, vitreous cell, chorioretinal scarring and vasculitis. Those can all happen in the setting of pseudophakic CME—albeit rarely.

"I also do very careful retinal exams," she continues. "I've seen post-cataract-surgery patients who develop a retinal vein occlusion or some other sort of occlusive event that comes with fluid, and it looks like pseudophakic CME. It's really important to rule those things out. I also look for other reasons for intraretinal and subretinal fluid. If the person has dry macular degeneration, have they converted to the wet kind? Should we get a fluorescein angiogram again and make sure there's no choroidal neovascularization?

"The point is that it's important to make sure that nothing else is going on in the eye," she concludes. "If some kind of active inflammation is happening, we need to figure out why it exists. We can treat it locally, but if the patient needs systemic treatment, we should be doing that as well. So I've learned to be very diligent about working these patients up." ◂

Presbyopic IOL Pipeline

(Continued from p. 30)

is its ability to allow focus to shift from very near to very far with just a fraction of a millimeter of diameter change. Preliminary results from bench studies performed by the company have demonstrated that the lens can achieve 6 D or greater accommodation with less than 0.2 mm of diameter change, and that it provides smooth and immediate transitions across all ranges (near, distance and intermediate) with minimal dysphotopsias and minimal effect on contrast sensitivity. [12]

"We have initial confirmation of this accommodation in preclinical work and are progressing to further clinical trials in the near future," says the company's CEO and president, Jim Ellis, MD, who reports that human studies are scheduled to begin this spring (2022). "The proof of concept has been validated with bench testing as well as *in vivo*."

Dr. Ellis adds, "Anyone with presbyopia would be a candidate for this IOL." He notes that the design of the JelliSee makes it a suitable lens for patients with ocular surface, retinal or macular disease who aren't typically ideal candidates for posterior chamber IOLs.

"Because the JelliSee IOL is a shape-changing monofocal lens, just like our natural lens when we were young, these contraindications don't apply," explains Dr. Ellis. He also notes that since the IOL is independent of retained capsular elasticity, its functionality should also not be affected by capsular fibrosis. ◂

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A woman presents with a recent onset of decreased vision and burning in her eye.

MARIUS HEERSINK, MD, AND ZEBA A. SYED, MD
PHILADELPHIA

Presentation and Initial Work-up

A 38-year-old Caucasian female presented with a one-day history of decreased vision and burning sensation in her right eye. Two days prior to presentation, she was planting flowers in her garden to attract more butterflies to her yard. She reported mild irritation in her right eye immediately after completing the yard work, which improved with lubrication. The next morning, she woke up with blurry vision followed by progressive foreign body sensation in her right eye. She also reported photophobia but denied headache, history of trauma, recent illness, or concurrent symptoms in the left eye. Systemic review was negative; the patient denied history of any cold sores, rashes, joint pain, new medications or the use of any eye drops.

Medical History

Our patient had a right dacryocystorhinostomy 10 years prior but denied any other past ocular history. Past medical history was significant only for GERD and mild iron-deficiency anemia, for which the patient takes omeprazole and an over-the-counter iron supplement daily. Family history and social history were also unremarkable.

Exam

Initial ocular examination demonstrated a best corrected visual acuity of 20/70 OD and 20/20 OS. External examination was normal with no rashes, edema or erythema. Extraocular motility, confrontational visual field testing, and pupillary exam were normal. Intraocular pressures were 14 mmHg bilaterally. Lid eversion of the right eye revealed mild conjunctival injection and a papillary reaction without any foreign body. The pH of the ocular surface was normal.

The patient's right cornea was uniformly edematous, with stromal haze and 2+ Descemet folds throughout *(See Figure 1)*. There was a small amount of scattered punctate epithelial erosions. The endothelium appeared otherwise normal, without any clear disruption of Descemet's membrane detectable by slit lamp. The left cornea was normal. No stromal infiltrate or keratic precipitates were observed in either eye. Her anterior chambers were deep and quiet in both eyes, and the remainder of the examination, including a dilated fundoscopic exam, was normal.

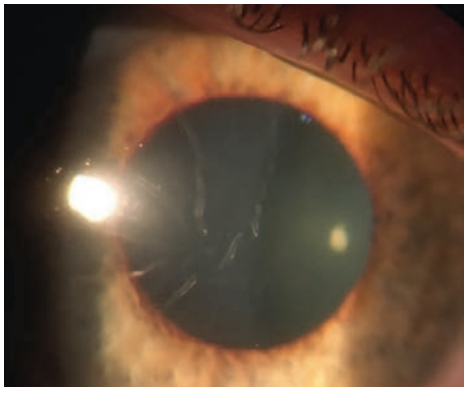

Figure 1. Slit lamp photo of the right eye on the day of presentation showing moderate Descemet's folds but an otherwise clear cornea.

What is your diagnosis? What further work-up would you pursue? The diagnosis appears on p. 64.

Work-up, Diagnosis and Treatment

Ancillary imaging was obtained, including Pentacam *(See Figure 2)*, specular microscopy *(See Figure 3)*, and anterior segment OCT *(See Figure 4)*. Pentacam revealed severe unilateral corneal edema. Endothelial cells were undetectable in the right eye by specular microscopy, while the left eye had an endothelial cell density of 2,439 cells/mm^2.

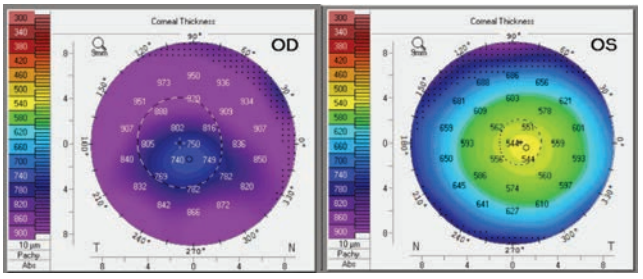

Figure 2. Corneal thickness by Pentacam of right and left eyes on day of presentation.

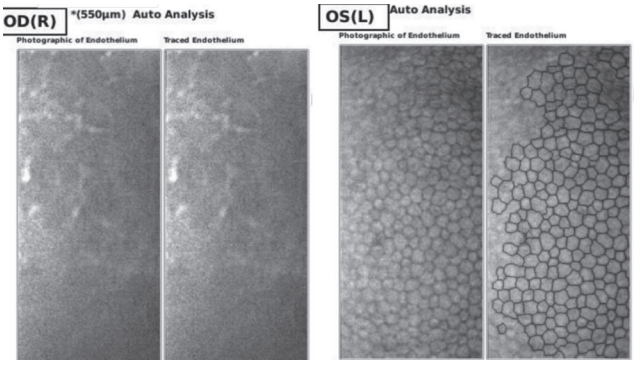

Figure 3. Endothelial cell density by specular microscopy of right and left eyes on day of presentation, demonstrating inadequate visualization of endothelial cells of the right eye and normal endothelium of the left eye.

The differential diagnosis for this patient with sudden onset of unilateral corneal edema includes endothelial dystrophy, infection, inflammation and metabolic etiologies. The presentation was not consistent with an endothelial dystrophy as the patient's age and sudden onset are atypical for a first presentation of endothelial dystrophy, her endothelium and stroma were clinically normal in both eyes, and the patient reliably denied any previous ophthalmic history.[1,2] Infectious and inflammatory causes such as a herpes simplex viral keratitis/endotheliitis or anterior uveitis were also considered, but the patient's complete lack of stromal, endothelial, or anterior chamber inflammation reduced the likelihood of these diagnoses. Upon a more detailed review of the patient's history, she revealed she was planting milkweed flowers and handling them without gloves, leading to a presumed diagnosis of corneal edema secondary to acute endothelial toxicity.

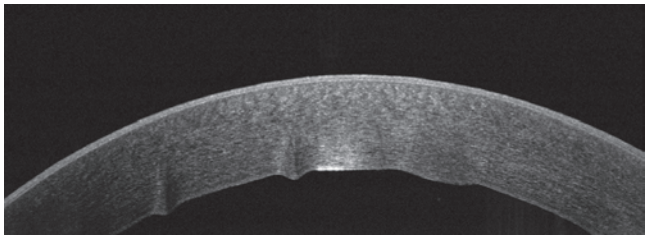

Figure 4. Anterior segment OCT of the right eye on the day of presentation, demonstrating stromal edema and Descemet folds.

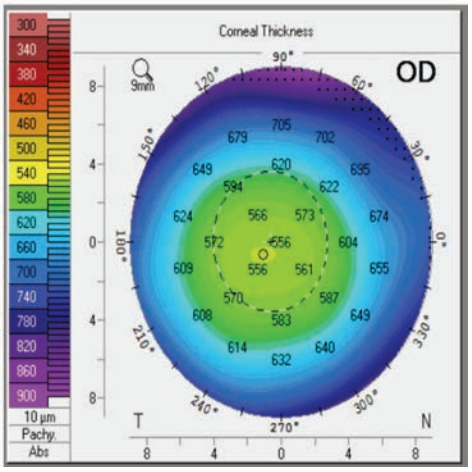

Figure 5. Corneal thickness by Pentacam of the right eye 10 days after initial presentation, showing resolution of corneal edema.

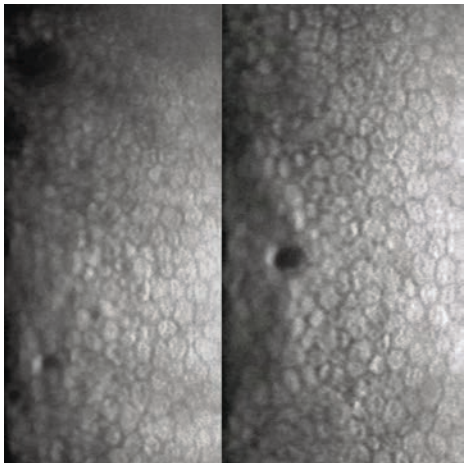

Figure 6. Endothelial cell density by specular microscopy of right and left eyes 10 days after initial presentation, demonstrating healthy-appearing endothelial cells in the right eye.

Her corneal edema in the right eye was empirically treated with loteprednol 0.5% every two hours while awake and with Muro 128 5% saline drops four times per day. The patient was also counseled on avoiding further milkweed exposure. She returned to clinic the next day and her vision and corneal edema had improved, but she complained of worsening foreign body sensation. Slit lamp examination revealed a new, 3-mm, ruptured central bulla without infiltrate. A bandage contact lens was placed and the patient continued the same drop regimen

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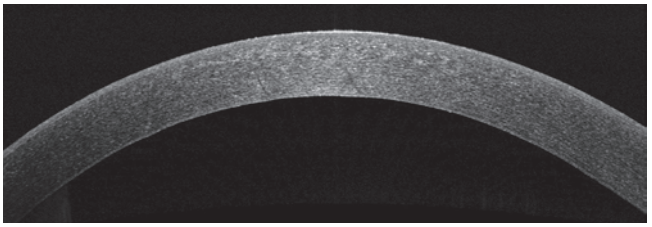

Figure 7. Anterior segment OCT of the right eye 10 days after first presentation, showing resolution of stromal edema and Descemet's folds.

with close follow-up. Two days later, her epithelial defect had closed and her corneal edema had further improved. Her bandage contact lens was then removed and her drops tapered, and within 10 days of initial presentation, her right eye's visual acuity returned to its baseline of 20/20. Repeat Pentacam, specular microscopy and anterior segment OCT showed rapid recovery, with endothelial cell density recovering to 2,349 cells/mm^2 in the right eye to match the left eye cell density of 2,439 cells/mm^2 *(See Figures 5, 6, 7).*

Discussion

Milkweed plants, formally known as plants belonging to the genus Asclepias, are relatively common wildflowers known for their ability to attract butterflies and other insects. In particular, the Monarch butterfly is drawn to the plant, making it an increasingly popular flower in many gardens.[3] Milkweed sap contains high levels of cardenolides, also known as cardiac glycosides, which inhibit the cellular sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) pump.[3,4] Digoxin, the cardiac inotropic medication, is an example of a low-dose cardiac glycoside used to increase heart function. However, cardiac glycosides are very potent cytotoxins and have been known to kill large animals when grazing on a single milkweed plant.[3,5] Interestingly, Monarch butterflies are unique among animals and have mutated Na^+/K^+-ATPase pumps that render them immune to cardenolides toxicity.[6,7]

In the eye, the endothelial cells that maintain corneal transparency are highly metabolically active and rely primarily on the Na^+/K^+-ATPase pump to dehydrate the cornea.[8,9] Both topical and systemic digoxin exposure cause dysfunction of endothelial cells, leading to rapid-onset corneal edema and bullous keratopathy.[9] In almost all cases, endothelial function returns within several days after cessation of cardenolide toxin exposure if the ensuing edema and inflammation can be controlled in the interim.[10,11]

Steroid drops play an important role in recovering from toxic corneal edema. Especially in younger patients, steroids protect endothelial cells during recovery by reducing cellular edema and inflammation.[9,13] Steroids have also been demonstrated to upregulate Na^+/K^+-ATPase pump activity, which could increase toxin clearance by the remaining functional endothelial cells.[12] Some cases even report using oral prednisone in addition to topical steroids to hasten endothelial recovery.[10,11] Muro 128 drops may also accelerate visual improvement by controlling corneal edema while the endothelium recovers.[9,13]

In summary, endothelial milkweed toxicity is increasingly common and difficult to diagnose, especially if the patient does not remember milkweed contact as even small amounts of cardenolide toxin exposure can cause significant endothelial dysfunction. The presentation can also be confused for decompensated Fuchs dystrophy or HSV endothelial keratitis, especially if advanced corneal imaging techniques are not available. Misdiagnosis may delay the use of steroids, which could worsen endothelial inflammation and cause permanent endothelial loss.[9] Fortunately, if long-standing endothelial edema and inflammation are avoided, patients generally make a full recovery within several days without long-term complications. ◀

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References: 1. US Department of Health and Human Services. XEN® Glaucoma Treatment System clearance letter. US FDA CDRH website. Published November 21, 2016. Accessed November 4, 2021. https://www.accessdata.fda.gov/cdrh_docs/pdf16/K161457.pdf. **2.** XEN® Directions for Use. **3.** Data on file, Allergan, 2016; Clinical Study Report R-020.

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